

ehp | CHILDREN'S HEALTH COLLECTION 2015

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OCTOBER 2014–SEPTEMBER 2015

www.ehponline.org

Disease Outcomes

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- Global Health

Methodologies *and* Populations

- Biomarkers and Biomonitoring
- Epigenetics
- Methodologies



PREFACE

Children's Health Collection 2015 comprises abstracts of all relevant articles published in *EHP* from October 2014 through September 2015: peer-reviewed research articles, news features, Science Selections, and editorials. Abstracts are featured for each research article published in an issue, and hyperlinks take readers directly to the full article online (<http://www.ehponline.org/>). The Science Selections are noted just below the related research.

As in previous Collections, the three main sections—Disease Outcomes, Exposures, and Methodologies and Populations—contain all research that has appeared in the Children's Health section of each *EHP* issue as well as relevant reviews and commentaries, research that involves both adult and child cohorts and both animal and human components, diseases with fetal or childhood origins, experimental models with direct application to children's health and pediatric practice, and topics of general interest to children's health researchers and advocates. Some specific topics (e.g., Food Safety, Insecurity, Nutrition) are featured in news articles but not in research.

New this year is the inclusion of Advance Publication articles—articles that have been accepted, but not yet copyedited and added to a specific issue—published online through September. These appear at the end of each topic area; each includes the doi information but not an abstract. The doi link will access the most recent form of the article, whether Advance Publication or the copyedited final version.

As developing topics, analyses of green (and blue) space show how these physical spaces provide benefits in, for example, birth weight and neurodevelopment as well as reductions in obesity; and analyses of multiple exposures reflect the complexity of interactions and outcomes. New categories are Natural Gas and Fracking, demonstrating this technique's potential health impacts and environmental damage, and Global Health. Besides the many articles in other sections that analyze data from around the world, Global Health includes an extensive review of various exposures throughout Latin America as well as efforts to address them, and a study of biomonitoring throughout Europe. In addition, studies that combine multiple cohorts (e.g., ESCAPE, NewGeneris), databases, methodologies, and analyses of multiple environmental factors and outcomes reflect efforts to harmonize data and address the variety of exposures and outcomes around the world. The Navigation Guide systematic reviews provide methods for synthesizing these data, and articles on climate change reflect trends that have global impact.

Please see <http://ehp.niehs.nih.gov/special-collections/> for all the yearly Children's Health collections.



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ASTHMA, RESPIRATORY DISEASE, LUNG DEVELOPMENT, ALLERGY

Perfluoroalkyl Chemicals and Asthma among Children 12–19 Years of Age: NHANES (1999–2008)

Olivier Humblet, Ledif Grisell Diaz-Ramirez, John R. Balmes, Susan M. Pinney,
and Robert A. Hiatt

122:1129–1133 (October 2014)

<http://dx.doi.org/10.1289/ehp.1306606>

Background: Perfluoroalkyl chemicals (PFCs) are a family of commonly used industrial chemicals whose persistence and ubiquity in human blood samples has led to concern about possible toxicity. Several animal studies and one recent human study have suggested a link between exposure to PFCs and asthma, although few epidemiologic studies have been conducted.

Objectives: We investigated children's PFC serum concentrations and their associations with asthma-related outcomes.

Methods: We evaluated the association between serum concentrations of eight PFCs, including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS), with self-reported lifetime asthma, recent wheezing, and current asthma using data from participants 12–19 years of age from the 1999–2000 and 2003–2008 National Health and Nutrition Examination Surveys.

Results: In multivariable-adjusted models, PFOA was associated with higher odds of ever having received a diagnosis of asthma [odds ratio (OR) = 1.18; 95% CI: 1.01, 1.39 for a doubling in PFOA], whereas for PFOS there were inverse relationships with both asthma and wheezing (OR = 0.88; 95% CI: 0.74, 1.04, and OR = 0.83; 95% CI: 0.67, 1.02, respectively). The associations were attenuated after accounting for sampling weights. No associations were seen between the other PFCs and any outcome.

Conclusions: This cross-sectional study provides some evidence for associations between exposure to PFCs and asthma-related outcomes in children. The evidence is inconsistent, however, and prospective studies are needed.

Asthma in Inner-City Children at 5–11 Years of Age and Prenatal Exposure to Phthalates: The Columbia Center for Children's Environmental Health Cohort

Robin M. Whyatt, Matthew S. Perzanowski, Allan C. Just, Andrew G. Rundle,
Kathleen M. Donohue, Antonia M. Calafat, Lori A. Hoepner, Frederica P. Perera,
and Rachel L. Miller

122:1141–1146 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307670>

Background: Studies suggest that phthalate exposures may adversely affect child respiratory health.

Objectives: We evaluated associations between asthma diagnosed in children between 5 and 11 years of age and prenatal exposures to butylbenzyl phthalate (BBzP), di-*n*-butyl phthalate (DnBP), di(2-ethylhexyl) phthalate (DEHP), and diethyl phthalate (DEP).

Methods: Phthalate metabolites were measured in spot urine collected from 300 pregnant inner-city women. Children were examined by an allergist or pulmonologist based on the first parental report of wheeze, other respiratory symptoms, and/or use of asthma rescue/controller medication in the preceding 12 months on repeat follow-up questionnaires. Standardized diagnostic criteria were used to classify these children as either having or not having current asthma at the time of the physician examination. Children without any report of wheeze or the other asthma-like symptoms were classified as nonasthmatics at the time of the last negative questionnaire. Modified Poisson regression analyses were used to estimate relative risks (RR) controlling for specific gravity and potential confounders.

Results: Of 300 children, 154 (51%) were examined by a physician because of reports of wheeze, other asthma-like symptoms, and/or medication use; 94 were diagnosed with current asthma and 60 without current asthma. The remaining 146 children were classified as nonasthmatic. Compared with levels in nonasthmatics, prenatal metabolites of BBzP and DnBP were associated with a history of asthma-like symptoms ($p < 0.05$) and with the diagnosis of current asthma: RR = 1.17 (95% CI: 1.01, 1.35) and RR = 1.25 (95% CI: 1.04, 1.51) per natural log-unit increase, respectively. Risk of current asthma was > 70% higher among children with maternal prenatal BBzP and DnBP metabolite concentrations in the third versus the first tertile.

Conclusion: Prenatal exposure to BBzP and DnBP may increase the risk of asthma among inner-city children. However, because this is the first such finding, results require replication.

Indoor Environmental Exposures and Exacerbation of Asthma: An Update to the 2000 Review by the Institute of Medicine

Watcharoot Kanchongkittiphon, Mark J. Mendell, Jonathan M. Gaffin, Grace Wang, and Wanda Phipatanakul

123:6–20 (January 2015)

<http://dx.doi.org/10.1289/ehp.1307922>

Background: Previous research has found relationships between specific indoor environmental exposures and exacerbation of asthma.

Objectives: In this review we provide an updated summary of knowledge from the scientific literature on indoor exposures and exacerbation of asthma.

Methods: Peer-reviewed articles published from 2000 to 2013 on indoor exposures and exacerbation of asthma were identified through PubMed, from reference lists, and from authors' files. Articles that focused on modifiable indoor exposures in relation to frequency or severity of exacerbation of asthma were selected for review. Research findings were reviewed and summarized with consideration of the strength of the evidence.

Results: Sixty-nine eligible articles were included. Major changed conclusions include a causal relationship with exacerbation for indoor dampness or dampness-related agents (in children); associations with exacerbation for dampness or dampness-related agents (in adults), endotoxin, and environmental tobacco smoke (in preschool children); and limited or suggestive evidence for association with exacerbation for indoor culturable *Penicillium* or total fungi, nitrogen dioxide, rodents (nonoccupational), feather/down pillows (protective relative to synthetic bedding), and (regardless of specific sensitization) dust mite, cockroach, dog, and dampness-related agents.

Discussion: This review, incorporating evidence reported since 2000, increases the strength of evidence linking many indoor factors to the exacerbation of asthma. Conclusions should be considered provisional until all available evidence is examined more thoroughly.

Conclusion: Multiple indoor exposures, especially dampness-related agents, merit increased attention to prevent exacerbation of asthma, possibly even in nonsensitized individuals. Additional research to establish causality and evaluate interventions is needed for these and other indoor exposures.

Early-life Exposure to Organophosphate Pesticides and Pediatric Respiratory Symptoms in the CHAMACOS Cohort

Rachel Raanan, Kim G. Harley, John R. Balmes, Asa Bradman, Michael Lipsett, and Brenda Eskenazi

123:179–185 (February 2015)

<http://dx.doi.org/10.1289/ehp.1408235>

Background: Although pesticide use is widespread, the possible effect of early-life exposure to organophosphate (OP) on pediatric respiratory health is not well described.

Objectives: We investigated the relationship between early-life exposure to OPs and respiratory outcomes.

Methods: Participants included 359 mothers and children from the CHAMACOS birth cohort. Dialkyl phosphate (DAP) metabolites of OP pesticides, specifically diethyl (DE) and dimethyl (DM) phosphate metabolites, were measured in urine from mothers twice during pregnancy (mean = 13 and 26 weeks gestation) and from children five times during childhood (0.5–5 years). Childhood DAP concentrations were estimated by the area under curve (AUC). Mothers reported their child's respiratory symptoms at 5 and 7 years of age. We used generalized estimating equations (GEE) to examine associations of prenatal and childhood DAP concentrations with repeated measures of respiratory symptoms and exercise-induced coughing at 5 and 7 years of age, adjusting for child's sex and age, maternal smoking during pregnancy, secondhand tobacco smoke, season of birth, PM_{2.5}, breastfeeding, mold and cockroaches in home, and distance from highway.

Results: Higher prenatal DAP concentrations, particularly DE, were nonsignificantly associated with respiratory symptoms in the previous 12 months at 5 or 7 years of age [adjusted odds ratio (aOR) per 10-fold increase = 1.44; 95% CI: 0.98, 2.12]. This association was strongest with total DAP and DE from the second half of pregnancy (aOR per 10-fold increase = 1.77; 95% CI: 1.06, 2.95; and 1.61; 95% CI: 1.08, 2.39, respectively). Childhood DAP, DE, and DM concentrations were associated with respiratory symptoms and exercise-induced coughing in the previous 12 months at 5 or 7 years of age (total DAPs: aOR per 10-fold increase = 2.53; 95% CI: 1.32, 4.86; and aOR = 5.40; 95% CI: 2.10, 13.91, respectively).

Conclusions: Early-life exposure to OP pesticides was associated with respiratory symptoms consistent with possible asthma in childhood.

Perinatal Exposure to Traffic-Related Air Pollution and Atopy at 1 Year of Age in a Multi-Center Canadian Birth Cohort Study

Hind Sbihi, Ryan W. Allen, Allan Becker, Jeffrey R. Brook, Piush Mandhane, James A. Scott, Malcolm R. Sears, Padmaja Subbarao, Tim K. Takaro, Stuart E. Turvey, and Michael Brauer

123:902–908 (September 2015)

<http://dx.doi.org/10.1289/ehp.1408700>

Background: The role of traffic-related air pollution (TRAP) exposure in the development of allergic sensitization in children is unclear, and few birth cohort studies have incorporated spatiotemporal exposure assessment.

Objectives: We aimed to examine the association between TRAP and atopy in 1-year-old children from an ongoing national birth cohort study in four Canadian cities.

Methods: We identified 2,477 children of approximately 1 year of age with assessment of atopy for inhalant (*Alternaria*, *Der p*, *Der f*, cat, dog, cockroach) and food-related (milk, eggs, peanuts, soy) allergens. Exposure to nitrogen dioxide (NO₂) was estimated from city-specific land use regression models accounting for residential mobility and temporal variability in ambient concentrations. We used mixed models to examine associations between atopy and exposure during pregnancy and the first year of life, including adjustment for covariates (maternal atopy, socioeconomic status, pets, mold, nutrition). We also conducted analyses stratified by time-location patterns, daycare attendance, and modeled home ventilation.

Results: Following spatiotemporal adjustment, TRAP exposure after birth increased the risk for development of atopy to any allergens [adjusted odds ratio (aOR) per 10 µg/m³ NO₂ = 1.16; 95% CI: 1.00, 1.41], but not during pregnancy (aOR = 1.02; 95% CI: 0.86, 1.22). This association was stronger among children not attending daycare (aOR = 1.61; 95% CI: 1.28, 2.01) compared with daycare attendees (aOR = 1.05; 95% CI: 0.81, 1.28). Trends to increased risk were also found for food (aOR = 1.17; 95% CI: 0.95, 1.47) and inhalant allergens (aOR = 1.28; 95% CI: 0.93, 1.76).

Conclusion: Using refined exposure estimates that incorporated temporal variability and residential mobility, we found that traffic-related air pollution during the first year of life was associated with atopy.

ADVANCE PUBLICATION | Urinary Dialkyl Phosphate Concentrations and Lung Function Parameters in Adolescents and Adults: Results from the Canadian Health Measures Survey

Ming Ye, Jeremy Beach, Jonathan W. Martin, and Ambikaipakan Senthilselvan

<http://dx.doi.org/10.1289/ehp.1509745>

NEURODEVELOPMENT, NEUROBEHAVIOR, INTELLIGENCE ASSESSMENT

Environmental Tobacco Smoke Exposure and Children's Intelligence at 8–11 Years of Age

Subin Park, Soo-Churl Cho, Yun-Chul Hong, Jae-Won Kim, Min-Sup Shin, Hee Jeong Yoo, Doug Hyun Han, Jae Hoon Cheong, and Bung-Nyun Kim

122:1123–1128 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307088>

Background: Evidence supporting a link between postnatal environmental tobacco smoke (ETS) exposure and cognitive problems among children is mounting, but inconsistent.

Objectives: We examined the relationship between ETS exposure, measured using urine cotinine, and IQ scores in Korean school-aged children.

Methods: The participants were 996 children 8–11 years of age recruited from five administrative regions in South Korea. We performed a cross-sectional analysis of urinary cotinine concentrations and IQ scores obtained using the abbreviated form of a Korean version of the Wechsler Intelligence Scales for Children. Associations were adjusted for potential confounders, and estimates were derived with and without adjustment for mother's Full-Scale IQ (FSIQ) score.

Results: After adjusting for sociodemographic and developmental covariates, urinary cotinine concentrations were inversely associated with FSIQ, Verbal IQ (VIQ), Performance IQ (PIQ), vocabulary, math, and block design scores. Following further adjustment for maternal IQ, only the VIQ scores remained significantly associated with urinary cotinine concentration ($B = -0.31$; 95% CI: $-0.60, -0.03$ for a 1-unit increase in natural log-transformed urine cotinine concentration; $p = 0.03$).

Conclusion: Urine cotinine concentrations were inversely associated with children's VIQ scores before and after adjusting for maternal IQ. Further prospective studies with serial measurements of cotinine are needed to confirm our findings.

Pyrethroid Pesticide Exposure and Parental Report of Learning Disability and Attention Deficit/Hyperactivity Disorder in U.S. Children: NHANES 1999–2002

Lesliam Quirós-Alcalá, Suril Mehta, and Brenda Eskenazi

122:1336–1342 (December 2014)

<http://dx.doi.org/10.1289/ehp.1308031>

Background: Use of pyrethroid insecticides has increased dramatically over the past decade; however, data on their potential health effects, particularly on children, are limited.

Objective: We examined the cross-sectional association between postnatal pyrethroid exposure and parental report of learning disability (LD) and attention deficit/hyperactivity disorder (ADHD) in children 6–15 years of age.

Methods: Using logistic regression, we estimated associations of urinary metabolites of pyrethroid insecticides with parent-reported LD, ADHD, and both LD and ADHD in 1,659–1,680 children participating in the National Health and Nutrition Examination Survey (1999–2002).

Results: The prevalence rates of parent-reported LD, ADHD, and both LD and ADHD were 12.7%, 10.0%, and 5.4%, respectively. Metabolite detection frequencies for 3-PBA [3-phenoxybenzoic acid], *cis*-DCCA [*cis*-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid], and *trans*-DCCA [*trans*-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid] were 77.1%, 35.6%, and 33.9%, respectively. The geometric mean 3-PBA concentration was 0.32 $\mu\text{g/L}$ (median = 0.31 $\mu\text{g/L}$; interquartile range = 0.10–0.89 $\mu\text{g/L}$). *cis*- and *trans*-DCCA 75th-percentile concentrations were 0.21 $\mu\text{g/L}$ and 0.68 $\mu\text{g/L}$, respectively. Log₁₀-transformed 3-PBA concentrations were associated with adjusted odds ratios (ORs) of 1.18 (95% CI: 0.92, 1.51) for parent-reported LD, 1.16 (95% CI: 0.85, 1.58) for ADHD, and 1.45 (95% CI: 0.92, 2.27) for both LD and ADHD. Adjusted ORs remained nonsignificant and decreased after controlling for creatinine and other environmental chemicals previously linked to altered neurodevelopment. Similarly, no significant associations were observed for *cis*- and *trans*-DCCA.

Conclusions: Postnatal pyrethroid exposure was not associated with parental report of LD and/or ADHD. Given the widespread and increasing use of pyrethroids, future research should evaluate exposures at current levels, particularly during critical windows of brain development.

Neurobehavioral Function in School-Age Children Exposed to Manganese in Drinking Water

Youssef Oulhote, Donna Mergler, Benoit Barbeau, David C. Bellinger, Thérèse Bouffard, Marie-Ève Brodeur, Dave Saint-Amour, Melissa Legrand, Sébastien Sauvé, and Maryse F. Bouchard

122:1343–1350 (December 2014)

<http://dx.doi.org/10.1289/ehp.1307918>

Background: Manganese neurotoxicity is well documented in individuals occupationally exposed to airborne particulates, but few data are available on risks from drinking-water exposure.

Objective: We examined associations of exposure from concentrations of manganese in water and hair with memory, attention, motor function, and parent- and teacher-reported hyperactive behaviors.

Methods: We recruited 375 children and measured manganese in home tap water (MnW) and hair (MnH). We estimated manganese intake from water ingestion. Using structural equation modeling, we estimated associations between neurobehavioral functions and MnH, MnW, and manganese intake from water. We evaluated exposure–response relationships using generalized additive models.

Results: After adjusting for potential confounders, a 1-SD increase in \log_{10} MnH was associated with a significant difference of –24% (95% CI: –36, –12%) SD in memory and –25% (95% CI: –41, –9%) SD in attention. The relations between \log_{10} MnH and poorer memory and attention were linear. A 1-SD increase in \log_{10} MnW was associated with a significant difference of –14% (95% CI: –24, –4%) SD in memory, and this relation was nonlinear, with a steeper decline in performance at MnW > 100 $\mu\text{g/L}$. A 1-SD increase in \log_{10} manganese intake from water was associated with a significant difference of –11% (95% CI: –21, –0.4%) SD in motor function. The relation between \log_{10} manganese intake and poorer motor function was linear. There was no significant association between manganese exposure and hyperactivity.

Conclusion: Exposure to manganese in water was associated with poorer neurobehavioral performances in children, even at low levels commonly encountered in North America.

Prenatal Organochlorine and Methylmercury Exposure and Memory and Learning in School-Age Children in Communities Near the New Bedford Harbor Superfund Site, Massachusetts

Sara T.C. Orenstein, Sally W. Thurston, David C. Bellinger, Joel D. Schwartz, Chitra J. Amarasinghwardena, Larisa M. Altshul, and Susan A. Korrick

122:1253–1259 (November 2014)

<http://dx.doi.org/10.1289/ehp.1307804>

Background: Polychlorinated biphenyls (PCBs), organochlorine pesticides, and methylmercury (MeHg) are environmentally persistent with adverse effects on neurodevelopment. However, especially among populations with commonly experienced low levels of exposure, research on neurodevelopmental effects of these toxicants has produced conflicting results.

Objectives: We assessed the association of low-level prenatal exposure to these contaminants with memory and learning.

Methods: We studied 393 children, born between 1993 and 1998 to mothers residing near a PCB-contaminated harbor in New Bedford, Massachusetts. Cord serum PCB, DDE (dichlorodiphenyldichloroethylene), and maternal peripartum hair mercury (Hg) levels were measured to estimate prenatal exposure. Memory and learning were assessed at 8 years of age (range, 7–11 years) using the Wide Range Assessment of Memory and Learning (WRAML), age-standardized to a mean \pm SD of 100 ± 15 . Associations with each WRAML index—Visual Memory, Verbal Memory, and Learning—were examined with multivariable linear regression, controlling for potential confounders.

Results: Although cord serum PCB levels were low (sum of four PCBs: mean, 0.3 ng/g serum; range, 0.01–4.4), hair Hg levels were typical of the U.S. fish-eating population (mean, 0.6 $\mu\text{g/g}$; range, 0.3–5.1). In multivariable models, each microgram per gram increase in hair Hg was associated with, on average, decrements of –2.8 on Visual Memory (95% CI: –5.0, –0.6, $p = 0.01$), –2.2 on Learning (95% CI: –4.6, 0.2, $p = 0.08$), and –1.7 on Verbal Memory (95% CI: –3.9, 0.6, $p = 0.14$). There were no significant adverse associations of PCBs or DDE with WRAML indices.

Conclusions: These results support an adverse relationship between low-level prenatal MeHg exposure and childhood memory and learning, particularly visual memory.

Prenatal Exposure to Phthalate Esters and Behavioral Syndromes in Children at 8 Years of Age: Taiwan Maternal and Infant Cohort Study

Yin-Ju Lien, Hsiu-Ying Ku, Pen-Hua Su, Suh-Jen Chen, Hsiao-Yen Chen, Pao-Chi Liao, Wei-J. Chen, and Shu-Li Wang

123:95–100 (January 2015)

<http://dx.doi.org/10.1289/ehp.1307154>

Background: Few studies have shown an association between prenatal phthalate exposure and adverse effects on neurodevelopment and behavior in young children.

Objectives: We aimed to assess the relationship between prenatal exposure to phthalate esters and behavior syndromes in children at 8 years of age.

Methods: A total of 122 mother–child pairs from the general population in central Taiwan were studied from 2000 to 2009. Mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), mono-butyl phthalate (MBP), mono-benzyl phthalate (MBzP), and three di-(2-ethylhexyl) phthalate (DEHP) metabolites—mono-2-ethylhexyl, mono-2-ethyl-5-hydroxyhexyl, and mono-2-ethyl-5-oxohexyl phthalates (MEHP, MEHHP, and MEOHP)—were measured in maternal urine collected during the third trimester of pregnancy using liquid chromatography–electrospray ionization–tandem mass spectrometry. Behavioral syndromes of children at 8 years of age were evaluated using the Child Behavior Checklist (CBCL). Associations between \log_{10} -transformed creatinine-corrected phthalate concentrations and standardized scores of the CBCL were estimated using linear regression models or multinomial logistic regressions with adjustments for potential confounders.

Results: Externalizing problem scores were significantly higher in association with a 1-unit increase in \log_{10} -transformed creatinine-corrected concentrations of maternal MBP ($\beta = 4.29$; 95% CI: 0.59, 7.99), MEOHP ($\beta = 3.74$; 95% CI: 1.33, 6.15), and MEHP ($\beta = 4.28$; 95% CI: 0.03, 8.26) after adjusting for the child's sex, intelligence, and family income. Meanwhile, MBP and MEOHP were significantly associated with Delinquent Behavior and Aggressive Behavior scores. The same pattern was found for borderline and/or clinical ranges.

Conclusions: Our findings suggest positive associations between maternal DEHP and dibutyl phthalate (DBP) exposure and externalizing domain behavior problems in 8-year-old children.

Environmental Lead Exposure and Attention Deficit/Hyperactivity Disorder Symptom Domains in a Community Sample of South Korean School-Age Children

Soon-Beom Hong, Mee-Hyang Im, Jae-Won Kim, Eun-Jin Park, Min-Sup Shin, Boong-Nyun Kim, Hee-Jeong Yoo, In-Hee Cho, Soo-Young Bhang, Yun-Chul Hong, and Soo-Churl Cho

123:271–276 (March 2015)

<http://dx.doi.org/10.1289/ehp.1307420>

Background: Low-level environmental exposure to lead has been associated with both reduced intelligence and symptoms of attention deficit/hyperactivity disorder (ADHD). However, few studies have estimated the association of lead and intelligence independent of ADHD, and it is not clear from previous studies whether lead is associated with both inattention and impulsivity ADHD symptoms.

Objectives: We estimated mutually adjusted associations of environmental lead exposure with both intelligence and ADHD symptoms, and associations between lead and specific ADHD-related domains.

Methods: Blood lead concentrations were measured in a general population of 1,001 children 8–11 years of age. We used multivariable linear regression models to estimate associations of blood lead concentrations with IQ scores, teacher and parent ratings of ADHD symptoms, and measures of inattention and impulsivity. Models were adjusted for demographic variables and other environmental exposures (blood levels of mercury and manganese, urinary concentrations of cotinine, phthalate metabolites, and bisphenol A).

Results: Associations of blood lead with lower IQ and higher impulsivity were robust to adjustment for a variety of covariates. When adjusted for demographic characteristics, other environmental exposures, and ADHD symptoms or IQ, a 10-fold increase in blood lead concentration was associated with lower Full-Scale IQ (–7.23; 95% CI: –13.39, –1.07) and higher parent- and teacher-rated hyperactivity/impulsivity scores (ADHD Rating Scale, 1.99; 95% CI: 0.17, 3.81 and 3.66; 95% CI: 1.18, 6.13, respectively) and commission errors (Continuous Performance Test, 12.27; 95% CI: –0.08, 24.62). Blood lead was not significantly associated with inattention in adjusted models.

Conclusions: Low-level lead exposure was adversely associated with intelligence in school-age children independent of ADHD, and environmental lead exposure was selectively associated with impulsivity among the clinical features of ADHD.

Attention Deficit/Hyperactivity Disorder and Childhood Autism in Association with Prenatal Exposure to Perfluoroalkyl Substances: A Nested Case–Control Study in the Danish National Birth Cohort

Zeyan Liew, Beate Ritz, Ondine S. von Ehrenstein, Bodil Hammer Bech, Ellen Aagaard Nohr, Chunyuan Fei, Rossana Bossi, Tine Brink Henriksen, Eva Cecilie Bonefeld-Jørgensen, and Jørn Olsen

123:367–373 (April 2015)
<http://dx.doi.org/10.1289/ehp.1408412>

Background: Perfluoroalkyl substances (PFASs) are persistent pollutants found to be endocrine disruptive and neurotoxic in animals. Positive correlations between PFASs and neurobehavioral problems in children were reported in cross-sectional data, but findings from prospective studies are limited.

Objectives: We investigated whether prenatal exposure to PFASs is associated with attention deficit/hyperactivity disorder (ADHD) or childhood autism in children.

Methods: Among 83,389 mother–child pairs enrolled in the Danish National Birth Cohort during 1996–2002, we identified 890 ADHD cases and 301 childhood autism cases from the Danish National Hospital Registry and the Danish Psychiatric Central Registry. From this cohort, we randomly selected 220 cases each of ADHD and autism, and we also randomly selected 550 controls frequency matched by child’s sex. Sixteen PFASs were measured in maternal plasma collected in early or mid-pregnancy. We calculated risk ratios (RRs) using generalized linear models, taking into account sampling weights.

Results: Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) were detected in all samples; four other PFASs were quantified in $\geq 90\%$ of the samples. We did not find consistent evidence of associations between mother’s PFAS plasma levels and ADHD [per natural log nanograms per milliliter increase: PFOS RR = 0.87 (95% CI: 0.74, 1.02); PFOA RR = 0.98 (95% CI: 0.82, 1.16)] or autism [per natural log nanograms per milliliter increase: PFOS RR = 0.92 (95% CI: 0.69, 1.22); PFOA RR = 0.98 (95% CI: 0.73, 1.31)]. We found positive as well as negative associations between higher PFAS quartiles and ADHD in models that simultaneously adjusted for all PFASs, but these estimates were imprecise.

Conclusions: In this study we found no consistent evidence to suggest that prenatal PFAS exposure increases the risk of ADHD or childhood autism in children.

Maternal Blood Manganese and Early Neurodevelopment: The Mothers and Children’s Environmental Health (MOCEH) Study

Soo Eun Chung, Hae-Kwan Cheong, Eun-Hee Ha, Boong-Nyun Kim, Mina Ha, Yangho Kim, Yun-Chul Hong, Hyesook Park, and Se-Young Oh

123:717–722 (July 2015)
<http://dx.doi.org/10.1289/ehp.1307865>

Background: Manganese is an essential trace element and common component of water, soil, and air. Prenatal manganese exposure may affect fetal and infantile neurodevelopment, but reports on *in utero* manganese exposure and infant neurodevelopment are rare.

Objective: This study was conducted to investigate a relationship between maternal blood manganese level and neurodevelopment of infants at 6 months of age.

Methods: Data were obtained from the Mothers and Children’s Environmental Health (MOCEH) birth cohort study. The study population included 232 pairs of pregnant women and their infants at 6 months of age. Maternal blood manganese was measured at term, just before delivery. Mental and psychomotor development in infancy was assessed at 6 months of age using the Bayley Scales of Infant Development. The relationship between maternal blood manganese level and the mental and psychomotor development indexes (MDI and PDI) was estimated for manganese modeled as a linear and as a categorical variable and using penalized splines for nonlinear modeling.

Results: Mean \pm SD maternal blood manganese concentration was 22.5 ± 6.5 $\mu\text{g/L}$. After adjustment for potential confounders, blood manganese was used as a continuous variable in a linear and nonlinear model. Associations between maternal blood manganese and MDI and PDI scores followed an inverted U-shape dose–response curve after adjustment for potential confounders, with lower scores associated with both low and high blood concentrations [MDI: likelihood-ratio test (LRT) $p = 0.075$, PDI: LRT $p = 0.038$]. Associations of both outcomes with increasing blood manganese shifted from positive to negative at concentrations of 24–28 $\mu\text{g/L}$ in this cohort of term, normal birth weight children.

Conclusion: Although no cut-off point has been established to define manganese toxicity, both high and low blood manganese levels may be associated with neurobehavioral function in infants.

Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ

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123:827–833 (August 2015)

<http://dx.doi.org/10.1289/ehp.1408554>

Background: Although prenatal methylmercury exposure has been linked to poorer intellectual function in several studies, data from two major prospective, longitudinal studies yielded contradictory results. Associations with cognitive deficits were reported in a Faroe Islands cohort, but few were found in a study in the Seychelles Islands. It has been suggested that co-exposure to another contaminant, polychlorinated biphenyls (PCBs), may be responsible for the positive findings in the former study and that co-exposure to nutrients in methylmercury-contaminated fish may have obscured and/or protected against adverse effects in the latter.

Objectives: We aimed to determine the degree to which co-exposure to PCBs may account for the adverse effects of methylmercury and the degree to which co-exposure to docosahexaenoic acid (DHA) may obscure these effects in a sample of Inuit children in Arctic Québec.

Methods: IQ was estimated in 282 school-age children from whom umbilical cord blood samples had been obtained and analyzed for mercury and other environmental exposures.

Results: Prenatal mercury exposure was related to poorer estimated IQ after adjustment for potential confounding variables. The entry of DHA into the model significantly strengthened the association with mercury, supporting the hypothesis that beneficial effects from DHA intake can obscure adverse effects of mercury exposure. Children with cord mercury ≥ 7.5 $\mu\text{g/L}$ were four times as likely to have an IQ score < 80 , the clinical cut-off for borderline intellectual disability. Co-exposure to PCBs did not alter the association of mercury with IQ.

Conclusions: To our knowledge, this is the first study to document an association of prenatal mercury exposure with poorer performance on a school-age assessment of IQ, a measure whose relevance for occupational success in adulthood is well established. This association was seen at levels in the range within which many U.S. children of Asian-American background are exposed.

Measured Prenatal and Estimated Postnatal Levels of Polychlorinated Biphenyls (PCBs) and ADHD-Related Behaviors in 8-Year-Old Children

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123:888–894 (September 2015)

<http://dx.doi.org/10.1289/ehp.1408084>

Background: Epidemiologic studies of postnatal PCB exposure and behavior have not reported consistent evidence of adverse associations, possibly because of challenges in exposure estimation. We previously developed a pharmacokinetic model to improve estimation of children's PCB exposure.

Objectives: We aimed to assess whether estimated serum PCB levels in infancy are associated with attention deficit/hyperactivity disorder (ADHD)-related behaviors at 8 years of age among children whose cord serum PCB levels were previously shown to be associated with ADHD-related behaviors.

Methods: We used a pharmacokinetic model to estimate monthly serum polychlorinated biphenyl (PCB)-153 levels in 441 infants (ages 1–12 months) based on parameters such as breastfeeding and cord serum PCB-153 levels. Behavior was evaluated at age 8 using the Conners' Rating Scale for Teachers (CRS-T). Associations between PCB-153 levels and ADHD-related CRS-T indices were assessed using multivariable quantile regression at the 50th and 75th percentiles of CRS-T scores, where higher percentiles reflect more adverse behaviors.

Results: Cord serum PCB-153 levels (median, 38 ng/g lipids) were associated with ADHD-related behaviors, although statistical significance was observed with quantile regression models only at the 75th percentile. Associations with postnatal exposure estimates were attenuated. For example, hyperactive-impulsive behavior scores at age 8 years were 0.9 points (95% CI: 0.2, 2.5), 0.5 points (95% CI: 0.3, 2.3), and 0.3 points (95% CI: –0.2, 1.5) higher in association with interquartile range increases in serum PCB-153 at birth, 2 months, and 12 months of age, respectively.

Conclusions: Associations between estimated postnatal PCB-153 exposures and ADHD-related behaviors at 8 years of age were weaker than associations with PCB-153 concentrations measured in cord serum at birth.

ADVANCE PUBLICATION | Exposure to Road Traffic Noise and Behavioral Problems in 7-Year-Old Children: A Cohort Study

Dorrit Hjortebjerg, Anne Marie Nybo Andersen, Jeppe Schultz Christensen, Matthias Ketzel, Ole Raaschou-Nielsen, Jordi Sunyer, Jordi Julvez, Joan Forn, and Mette Sørensen

<http://dx.doi.org/10.1289/ehp.1409430>

ADVANCE PUBLICATION | Traffic-Related Air Pollution, Noise at School, and Behavioral Problems in Barcelona Schoolchildren: A Cross-Sectional Study

Joan Forn, Payam Dadvand, Maria Foraster, Mar Alvarez-Pedrerol, Ioar Rivas, Mònica López-Vicente, Elisabet Suades-Gonzalez, Raquel Garcia-Esteban, Mikel Esnaola, Marta Cirach, James Grellier, Xavier Basagaña, Xavier Querol, Mònica Guxens, Mark J. Nieuwenhuijsen, and Jordi Sunyer

<http://dx.doi.org/10.1289/ehp.1409449>

ADVANCE PUBLICATION | Prenatal Organophosphorus Pesticide Exposure and Child Neurodevelopment at 24 Months: An Analysis of Four Birth Cohorts

Stephanie M. Engel, Asa Bradman, Mary S. Wolff, Virginia A. Rauh, Kim G. Harley, Jenny H. Yang, Lori A. Hoepner, Dana Boyd Barr, Kimberly Yoltan, Michelle G. Vedar, Yingying Xu, Richard W. Hornung, James G. Wetmur, Jia Chen, Nina T. Holland, Frederica P. Perera, Robin M. Whyatt, Bruce P. Lanphear, and Brenda Eskenazi

<http://dx.doi.org/10.1289/ehp.1409474>

ADVANCE PUBLICATION | Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother–Child PELAGIE Cohort (France)

Chloé Cartier, Charline Warembourg, Gaïd Le Maner-Idrissi, Agnès Lacroix, Florence Rouget, Christine Monfort, Gwendolina Limon, Gaël Durand, Dave Saint-Amour, Sylvaine Cordier, and Cécile Chevrier

<http://dx.doi.org/10.1289/ehp.1409472>

AUTISM

Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study

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122:1103–1109 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307044>

Background: Gestational exposure to several common agricultural pesticides can induce developmental neurotoxicity in humans, and has been associated with developmental delay and autism.

Objectives: We evaluated whether residential proximity to agricultural pesticides during pregnancy is associated with autism spectrum disorders (ASD) or developmental delay (DD) in the Childhood Autism Risks from Genetics and Environment (CHARGE) study.

Methods: The CHARGE study is a population-based case–control study of ASD, DD, and typical development. For 970 participants, commercial pesticide application data from the California Pesticide Use Report (1997–2008) were linked to the addresses during pregnancy. Pounds of active ingredient applied for organophosphates, organochlorines, pyrethroids, and carbamates were aggregated within 1.25-km, 1.5-km, and 1.75-km buffer distances from the home. Multinomial logistic regression was used to estimate the odds ratio (OR) of exposure comparing confirmed cases of ASD ($n = 486$) or DD ($n = 168$) with typically developing referents ($n = 316$).

Results: Approximately one-third of CHARGE study mothers lived, during pregnancy, within 1.5 km (just under 1 mile) of an agricultural pesticide application. Proximity to organophosphates at some point during gestation was associated with a 60% increased risk for ASD, higher for third-trimester exposures (OR = 2.0; 95% CI: 1.1, 3.6), and second-trimester chlorpyrifos applications (OR = 3.3; 95% CI: 1.5, 7.4). Children of mothers residing near pyrethroid insecticide applications just before conception or during third trimester were at greater risk for both ASD and DD, with ORs ranging from 1.7 to 2.3. Risk for DD was increased in those near carbamate applications, but no specific vulnerable period was identified.

Conclusions: This study of ASD strengthens the evidence linking neurodevelopmental disorders with gestational pesticide exposures, particularly organophosphates, and provides novel results of ASD and DD associations with, respectively, pyrethroids and carbamates.

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Pesticides and Autism Spectrum Disorders: New Findings from the CHARGE Study

David C. Holzman | A280 (October 2014)

<http://dx.doi.org/10.1289/ehp.122-A280>

Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case–Control Analysis within the Nurses' Health Study II Cohort

Raanan Raz, Andrea L. Roberts, Kristen Lyall, Jaime E. Hart, Allan C. Just, Francine Laden, and Marc G. Weisskopf

123:264–270 (March 2015)

<http://dx.doi.org/10.1289/ehp.1408133>

Background: Autism spectrum disorder (ASD) is a developmental disorder with increasing prevalence worldwide, yet has unclear etiology.

Objective: We explored the association between maternal exposure to particulate matter (PM) air pollution and odds of ASD in her child.

Methods: We conducted a nested case–control study of participants in the Nurses' Health Study II (NHS II), a prospective cohort of 116,430 U.S. female nurses recruited in 1989, followed by biennial mailed questionnaires. Subjects were NHS II participants' children born 1990–2002 with ASD ($n = 245$), and children without ASD ($n = 1,522$) randomly selected using frequency matching for birth years. Diagnosis of ASD was based on maternal report, which was validated against the Autism Diagnostic Interview-Revised in a subset. Monthly averages of PM with diameters $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and $2.5\text{--}10 \mu\text{m}$ ($\text{PM}_{10\text{--}2.5}$) were predicted from a spatiotemporal model for the continental United States and linked to residential addresses.

Results: $\text{PM}_{2.5}$ exposure during pregnancy was associated with increased odds of ASD, with an adjusted odds ratio (OR) for ASD per interquartile range (IQR) higher $\text{PM}_{2.5}$ ($4.42 \mu\text{g}/\text{m}^3$) of 1.57 (95% CI: 1.22, 2.03) among women with the same address before and after pregnancy (160 cases, 986 controls). Associations with $\text{PM}_{2.5}$ exposure 9 months before or after the pregnancy were weaker in independent models and null when all three time periods were included, whereas the association with the 9 months of pregnancy remained (OR = 1.63; 95% CI: 1.08, 2.47). The association between ASD and $\text{PM}_{2.5}$ was stronger for exposure during the third trimester (OR = 1.42 per IQR increase in $\text{PM}_{2.5}$; 95% CI: 1.09, 1.86) than during the first two trimesters (ORs = 1.06 and 1.00) when mutually adjusted. There was little association between $\text{PM}_{10\text{--}2.5}$ and ASD.

Conclusions: Higher maternal exposure to $\text{PM}_{2.5}$ during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.

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Air Pollution and ASDs: Homing In on an Environmental Risk Factor

Carrie Arnold | A68 (March 2015)

<http://dx.doi.org/10.1289/ehp.123-A68>

ADVANCE PUBLICATION | Air Pollution Exposure during Pregnancy and Childhood Autistic Traits in Four European Population-Based Cohort Studies: The ESCAPE Project

Mònica Guxens, Akhgar Ghassabian, Tong Gong, Raquel Garcia-Esteban, Daniela Porta, Lise Giorgis-Allemand, Catarina Almqvist, Aritz Aranbarri, Rob Beelen, Chiara Badaloni, Giulia Cesaroni, Audrey de Nazelle, Marisa Estarlich, Francesco Forastiere, Joan Forn, Ulrike Gehring, Jesús Ibarluzea, Vincent W.V. Jaddoe, Michal Korek, Paul Lichtenstein, Mark J. Nieuwenhuijsen, Marisa Rebagliato, Rémy Slama, Henning Tiemeier, Frank C. Verhulst, Heather E. Volk, Göran Pershagen, Bert Brunekreef, and Jordi Sunyer

<http://dx.doi.org/10.1289/ehp.1408483>

CANCERS

Residential Levels of Polybrominated Diphenyl Ethers and Risk of Childhood Acute Lymphoblastic Leukemia in California

Mary H. Ward, Joanne S. Colt, Nicole C. Deziel, Todd P. Whitehead, Peggy Reynolds, Robert B. Gunier, Marcia Nishioka, Gary V. Dahl, Stephen M. Rappaport, Patricia A. Buffler, and Catherine Metayer

122:1110–1116 (October 2014)

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Background: House dust is a major source of exposure to polybrominated diphenyl ethers (PBDEs), which are found at high levels in U.S. homes.

Methods: We studied 167 acute lymphoblastic leukemia (ALL) cases 0–7 years of age and 214 birth certificate controls matched on date of birth, sex, and race/ethnicity from the Northern California Childhood Leukemia Study. In 2001–2007, we sampled carpets in the room where the child spent the most time while awake; we used a high-volume small-surface sampler or we took dust from the home vacuum. We measured concentrations of 14 PBDE congeners including penta (28, 47, 99, 100, 153, 154), octa (183, 196, 197, 203), and decaBDEs (206–209). Odds ratios (ORs) were calculated using logistic regression, adjusting for demographics, income, year of dust collection, and sampling method.

Results: BDE-47, BDE-99, and BDE-209 were found at the highest concentrations (medians, 1,173, 1,579, and 938 ng/g, respectively). Comparing the highest to lowest quartile, we found no association with ALL for summed pentaBDEs (OR = 0.7; 95% CI: 0.4, 1.3), octaBDEs (OR = 1.3; 95% CI: 0.7, 2.3), or decaBDEs (OR = 1.0; 95% CI: 0.6, 1.8). Comparing homes in the highest concentration (nanograms per gram) tertile to those with no detections, we observed significantly increased ALL risk for BDE-196 (OR = 2.1; 95% CI: 1.1, 3.8), BDE-203 (OR = 2.0; 95% CI: 1.1, 3.6), BDE-206 (OR = 2.1; 95% CI: 1.1, 3.9), and BDE-207 (OR = 2.0; 95% CI: 1.03, 3.8).

Conclusion: We found no association with ALL for common PBDEs, but we observed positive associations for specific octa and nonaBDEs. Additional studies with repeated sampling and biological measures would be informative.

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Zeroing In on a Risk Factor? PBDE Exposure and Acute Lymphoblastic Leukemia

Tanya Tillett | A282 (October 2014)

<http://dx.doi.org/10.1289/ehp.122-A282>

BIRTH DEFECTS

Prenatal Phthalate Exposures and Anogenital Distance in Swedish Boys

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123:101–107 (January 2015)

<http://dx.doi.org/10.1289/ehp.1408163>

Background: Phthalates are used as plasticizers in soft polyvinyl chloride (PVC) and in a large number of consumer products. Because of reported health risks, diisononyl phthalate (DiNP) has been introduced as a replacement for di(2-ethylhexyl) phthalate (DEHP) in soft PVC. This raises concerns because animal data suggest that DiNP may have antiandrogenic properties similar to those of DEHP. The anogenital distance (AGD)—the distance from the anus to the genitals—has been used to assess reproductive toxicity.

Objective: The objective of this study was to examine the associations between prenatal phthalate exposure and AGD in Swedish infants.

Methods: AGD was measured in 196 boys at 21 months of age, and first-trimester urine was analyzed for 10 phthalate metabolites of DEP (diethyl phthalate), DBP (dibutyl phthalate), DEHP, BBzP (benzylbutyl phthalate), as well as DiNP and creatinine. Data on covariates were collected by questionnaires.

Results: The most significant associations were found between the shorter of two AGD measures (anoscrotal distance; AGD_{as}) and DiNP metabolites and strongest for oh-MMeOP [mono-(4-methyl-7-hydroxyoctyl) phthalate] and oxo-MMeOP [mono-(2-ethyl-5-oxohexyl) phthalate]. However, the AGD_{as} reduction was small (4%) in relation to more than an interquartile range increase in DiNP exposure.

Conclusions: These findings call into question the safety of substituting DiNP for DEHP in soft PVC, particularly because a shorter male AGD has been shown to relate to male genital birth defects in children and impaired reproductive function in adult males and the fact that human levels of DiNP are increasing globally.

ADVANCE PUBLICATION | Perfluorooctane Sulfonate Concentrations in Amniotic Fluid, Biomarkers of Fetal Leydig Cell Function, and Cryptorchidism and Hypospadias in Danish Boys (1980-1996)

Gunnar Toft, Bo A.G. Jönsson, Jens Peter Bonde, Bent Nørgaard-Pedersen, David M. Hougaard, Arie Cohen, Christian H. Lindh, Richard Ivell, Ravinder Anand-Ivell, and Morten S. Lindhard

<http://dx.doi.org/10.1289/ehp.1409288>

ADVANCE PUBLICATION | Organic Food Consumption during Pregnancy and Hypospadias and Cryptorchidism at Birth: The Norwegian Mother and Child Cohort Study (MoBa)

Anne Lise Brantsæter, Hanne Torjusen, Helle Margrete Meltzer, Eleni Papadopoulou, Jane A. Hoppin, Jan Alexander, Geir Lieblein, Gun Roos, Jon Magne Holten, Jackie Swartz, and Margaretha Haugen

<http://dx.doi.org/10.1289/ehp.1409518>

EYES AND EARS

Prenatal and Postnatal Serum PCB Concentrations and Cochlear Function in Children at 45 Months of Age

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122:1246–1252 (November 2014)

<http://dx.doi.org/10.1289/ehp.1307473>

Background: Some experimental and human data suggest that exposure to polychlorinated biphenyls (PCBs) may induce ototoxicity, though results of previous epidemiologic studies are mixed and generally focus on either prenatal or postnatal PCB concentrations exclusively.

Objectives: Our aim was to evaluate the association between pre- and postnatal PCB concentrations in relation to cochlear status, assessed by distortion product otoacoustic emissions (DPOAEs), and to further clarify the critical periods in development where cochlear status may be most susceptible to PCBs.

Methods: A total of 351 children from a birth cohort in eastern Slovakia underwent otoacoustic testing at 45 months of age. Maternal pregnancy, cord, and child 6-, 16-, and 45-month blood samples were collected and analyzed for PCB concentrations. At 45 months of age, DPOAEs were assessed at 11 frequencies in both ears. Multivariate, generalized linear models were used to estimate the associations between PCB concentrations at different ages and DPOAEs, adjusting for potential confounders.

Results: Maternal and cord PCB-153 concentrations were not associated with DPOAEs at 45 months. Higher postnatal PCB concentrations at 6-, 16-, and 45-months of age were associated with lower (poorer) DPOAE amplitudes. When all postnatal PCB exposures were considered as an area-under-the-curve metric, an increase in PCB-153 concentration from the 25th to the 75th percentile was associated with a 1.6-dB SPL (sound pressure level) decrease in DPOAE amplitude (95% CI: –2.6, –0.5; $p = 0.003$).

Conclusions: In this study, postnatal rather than maternal or cord PCB concentrations were associated with poorer performance on otoacoustic tests at age 45 months.

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PCBs and Impaired Cochlear Function in Children: Comparing Pre- and Postnatal Exposures

Julia R. Barrett | A310 (November 2014)

<http://dx.doi.org/10.1289/ehp.122-A310>

PREGNANCY OUTCOMES: PRETERM BIRTH, SMALL FOR GESTATIONAL AGE, FETAL DEVELOPMENT, PREGNANCY LOSS

Preconception Maternal and Paternal Exposure to Persistent Organic Pollutants and Birth Size: The LIFE Study

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123:88–94 (January 2015)
<http://dx.doi.org/10.1289/ehp.1308016>

Background: Persistent organic pollutants (POPs) are developmental toxicants, but the impact of both maternal and paternal exposures on offspring birth size is largely unexplored.

Objective: We examined associations between maternal and paternal serum concentrations of 63 POPs, comprising five major classes of pollutants, with birth size measures.

Methods: Parental serum concentrations of 9 organochlorine pesticides, 1 polybrominated biphenyl (PBB), 7 perfluoroalkyl chemicals (PFCs), 10 polybrominated diphenyl ethers (PBDEs), and 36 polychlorinated biphenyls (PCBs) were measured before conception for 234 couples. Differences in birth weight, length, head circumference, and ponderal index were estimated using multiple linear regression per 1-SD increase in natural log-transformed (ln-transformed) chemicals. Models were estimated separately for each parent and adjusted for maternal age, maternal prepregnancy body mass index (kilograms per meter squared) and other confounders, and all models included an interaction term between infant sex and each chemical.

Results: Among girls ($n = 117$), birth weight was significantly lower (range, 84–195 g) in association with a 1-SD increase in ln-transformed maternal serum concentrations of DDT, PBDE congeners 28 and 183, and paternal serum concentrations of PBDE-183 and PCB-167. Among boys ($n = 113$), maternal (PCBs 138, 153, 167, 170, 195, and 209 and perfluorooctane sulfonamide) and paternal (PCBs 172 and 195) serum concentrations of several POPs were statistically associated with lower birth weight (range, 98–170 g), whereas paternal concentrations of PBDEs (66, 99) were associated with higher birth weight. Differences in offspring head circumference, length, and ponderal index were also associated with parental exposures.

Conclusions: Preconceptional maternal and paternal concentrations of several POPs were associated with statistically significant differences in birth size among offspring.

Paternal Urinary Concentrations of Parabens and Other Phenols in Relation to Reproductive Outcomes among Couples from a Fertility Clinic

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123:665–671 (July 2015)
<http://dx.doi.org/10.1289/ehp.1408605>

Background: Human exposure to phenols, including bisphenol A and parabens, is widespread. Evidence suggests that paternal exposure to environmental chemicals may adversely affect reproductive outcomes.

Objectives: We evaluated associations of paternal phenol urinary concentrations with fertilization rate, embryo quality, implantation, and live birth.

Methods: Male–female couples who underwent *in vitro* fertilization (IVF) and/or intrauterine insemination (IUI) cycles in a prospective study of environmental determinants of fertility and pregnancy outcomes were included. The geometric mean of males' specific gravity–adjusted urinary phenol concentrations measured before females' cycle was quantified. Associations between male urinary phenol concentrations and fertilization rate, embryo quality, implantation, and live birth were investigated using generalized linear mixed models to account for multiple cycles per couple.

Results: Couples ($n = 218$) underwent 195 IUI and 211 IVF cycles. Paternal phenol concentrations were not associated with fertilization or live birth following IVF. In adjusted models, compared with the lowest quartile of methyl paraben, paternal concentrations in the second quartile were associated with decreased odds of live birth following IUI (adjusted odds ratio = 0.19; 95% CI: 0.04, 0.82).

Conclusions: To our knowledge, these are some of the first data on the association of paternal urinary phenol concentrations with reproduction and pregnancy outcomes. Although these results do not preclude possible adverse effects of paternal paraben exposures on such outcomes, given the modest sample size, further understanding could result from confirmation using a larger and more diverse population.

Urinary Bisphenol A Levels during Pregnancy and Risk of Preterm Birth

David E. Cantonwine, Kelly K. Ferguson, Bhramar Mukherjee, Thomas F. McElrath, and John D. Meeker

123:895–901 (September 2015)
<http://dx.doi.org/10.1289/ehp.1408126>

Background: Preterm birth (PTB), a leading cause of infant mortality and morbidity, has a complex etiology with a multitude of interacting causes and risk factors. The role of environmental contaminants, particularly bisphenol A (BPA), is understudied with regard to PTB.

Objectives: In the present study we examined the relationship between longitudinally measured BPA exposure during gestation and PTB.

Methods: A nested case–control study was performed from women enrolled in a prospective birth cohort study at Brigham and Women's Hospital in Boston, Massachusetts, during 2006–2008. Urine samples were analyzed for BPA concentrations at a minimum of three time points during pregnancy on 130 cases of PTB and 352 randomly assigned controls. Clinical classifications of PTB were defined as “spontaneous,” which was preceded by spontaneous preterm labor or preterm premature rupture of membranes, or “placental,” which was preceded by preeclampsia or intrauterine growth restriction.

Results: Geometric mean concentrations of BPA did not differ significantly between cases and controls. In adjusted models, urinary BPA averaged across pregnancy was not significantly associated with PTB. When examining clinical classifications of PTB, urinary BPA late in pregnancy was significantly associated with increased odds of delivering a spontaneous PTB. After stratification on infant's sex, averaged BPA exposure during pregnancy was associated with significantly increased odds of being delivered preterm among females, but not males.

Conclusions: These results provide little evidence of a relationship between BPA and prematurity, though further research may be warranted given the generalizability of participant recruitment from a tertiary teaching hospital, limited sample size, and significant associations among females and within the clinical subcategories of PTB.

ADVANCE PUBLICATION | Geographic Variation in the Association between Ambient Fine Particulate Matter (PM_{2.5}) and Term Low Birth Weight in the United States

Yongping Hao, Heather Strosnider, Lina Balluz, and Judith R. Qualters
<http://dx.doi.org/10.1289/ehp.1408798>

ADVANCE PUBLICATION | Associations of Pregnancy Outcomes and PM_{2.5} in a National Canadian Study

David M. Stieb, Li Chen, Bernardo S. Beckerman, Michael Jerrett, Daniel L. Crouse, D. Walter Rasugu Omariba, Paul A. Peters, Aaron van Donkelaar, Randall V. Martin, Richard T. Burnett, Nicolas L. Gilbert, Michael Tjepkema, Shiliang Liu, and Rose M. Dugandzic
<http://dx.doi.org/10.1289/ehp.1408995>

ADVANCE PUBLICATION | Prenatal Exposure to NO₂ and Ultrasound Measures of Fetal Growth in the Spanish INMA Cohort

Carmen Iñiguez, Ana Esplugues, Jordi Sunyer, Mikel Basterrechea, Ana Fernández-Somoano, Olga Costa, Marisa Estarlich, Inmaculada Aguilera, Aitana Lertxundi, Adonina Tardón, Mònica Guxens, Mario Murcia, Maria-Jose Lopez-Espinosa, and Ferran Ballester, on behalf of the INMA Project
<http://dx.doi.org/10.1289/ehp.1409423>

ADVANCE PUBLICATION | Cord Blood Methylmercury and Fetal Growth Outcomes in Baltimore Newborns: Potential Confounding and Effect Modification by Omega-3 Fatty Acids, Selenium, and Sex

Ellen M. Wells, Julie B. Herbstman, Yu Hong Lin, Jeffery Jarrett, Carl P. Verdon, Cynthia Ward, Kathleen L. Caldwell, Joseph R. Hibbeln, Frank R. Witter, Rolf U. Halden, and Lynn R. Goldman
<http://dx.doi.org/10.1289/ehp.1408596>

ADVANCE PUBLICATION | Exposure to Bisphenol A and Phthalates during Pregnancy and Ultrasound Measures of Fetal Growth in the INMA-Sabadell Cohort

Maribel Casas, Damaskini Valvi, Ana Ballesteros-Gomez, Mireia Gascon, Mariana F. Fernández, Raquel Garcia-Esteban, Carmen Iñiguez, David Martínez, Mario Murcia, Nuria Monfort, Noelia Luque, Soledad Rubio, Rosa Ventura, Jordi Sunyer, and Martine Vrijheid
<http://dx.doi.org/10.1289/ehp.1409190>

ADVANCE PUBLICATION | Urinary Concentrations of Phthalate Metabolites and Bisphenol A and Associations with Follicular-Phase Length, Luteal-Phase Length, Fecundability, and Early Pregnancy Loss

Anne Marie Jukic, Antonia M. Calafat, D. Robert McConaughy, Matthew P. Longnecker, Jane A. Hoppin, Clarice R. Weinberg, Allen J. Wilcox, and Donna D. Baird
<http://dx.doi.org/10.1289/ehp.1408164>

ADVANCE PUBLICATION | Blood Biomarkers of Late Pregnancy Exposure to Trihalomethanes in Drinking Water and Fetal Growth Measures and Gestational Age in a Chinese Cohort

Wen-Cheng Cao, Qiang Zeng, Yan Luo, Hai-Xia Chen, Dong-Yue Miao, Li Li, Ying-Hui Cheng, Min Li, Fan Wang, Ling You, Yi-Xin Wang, Pan Yang, and Wen-Qing Lu

<http://dx.doi.org/10.1289/ehp.1409234>

ADVANCE PUBLICATION | Prenatal Ambient Air Pollution, Placental Mitochondrial DNA Content, and Birth Weight in the INMA (Spain) and ENVIRONAGE (Belgium) Birth Cohorts

Diana B.P. Clemente, Maribel Casas, Nadia Vilahur, Haizea Begiristain, Mariona Bustamante, Anne-Elie Carsin, Mariana F. Fernández, Frans Fierens, Wilfried Gyselaers, Carmen Iñiguez, Bram G. Janssen, Wouter Lefebvre, Sabrina Llop, Nicolás Olea, Marie Pedersen, Nicky Pieters, Loreto Santa Marina, Ana Souto, Adonina Tardón, Charlotte Vanpoucke, Martine Vrijheid, Jordi Sunyer, and Tim S. Nawrot

<http://dx.doi.org/10.1289/ehp.1408981>

INFECTIONS

ADVANCE PUBLICATION | Infant Infections and Respiratory Symptoms in Relation to *in Utero* Arsenic Exposure in a U.S. Cohort

Shohreh F. Farzan, Zhigang Li, Susan A. Korrick, Donna Spiegelman, Richard Enelow, Kari Nadeau, Emily Baker, and Margaret R. Karagas

<http://dx.doi.org/10.1289/ehp.1409282>

FETAL OR EARLY-LIFE EXPOSURES CONTRIBUTING TO LATER CHILDHOOD OR ADULT DISEASE

ADVANCE PUBLICATION | Prenatal Exposure to Perfluoroalkyl Acids and Serum Testosterone Concentrations at 15 Years of Age in Female ALSPAC Study Participants

Mildred Maisonet, Antonia M. Calafat, Michele Marcus, Jouni J.K. Jaakkola, and Hany Lashen

<http://dx.doi.org/10.1289/ehp.1408847>

ADVANCE PUBLICATION | Mechanisms Underlying Latent Disease Risk Associated with Early-Life Arsenic Exposure: Current Research Trends and Scientific Gaps

Kathryn A. Bailey, Allan H. Smith, Erik J. Tokar, Joseph H. Graziano, Kyoung-Woong Kim, Panida Navasumrit, Mathuros Ruchirawat, Apinya Thiantanawat, William A. Suk, and Rebecca C. Fry

<http://dx.doi.org/10.1289/ehp.1409360>

ADVANCE PUBLICATION | Lead Exposure during Early Human Development and DNA Methylation of Imprinted Gene Regulatory Elements in Adulthood

Yue Li, Changchun Xie, Susan K. Murphy, David Skaar, Monica Nye, Adriana C. Vidal, Kim M. Cecil, Kim N. Dietrich, Alvaro Puga, Randy L. Jirtle, and Cathrine Hoyø

<http://dx.doi.org/10.1289/ehp.1408577>

INFANT AND CHILDHOOD GROWTH AND OBESITY

A Longitudinal Cohort Study of Body Mass Index and Childhood Exposure to Secondhand Tobacco Smoke and Air Pollution: The Southern California Children's Health Study

Rob McConnell, Ernest Shen, Frank D. Gilliland, Michael Jerrett, Jennifer Wolch, Chih-Chieh Chang, Frederick Lurmann, and Kiros Berhane

123:360–366 (April 2015)

<http://dx.doi.org/10.1289/ehp.1307031>

Background: Childhood body mass index (BMI) and obesity prevalence have been associated with exposure to secondhand smoke (SHS), maternal smoking during pregnancy, and vehicular air pollution. There has been little previous study of joint BMI effects of air pollution and tobacco smoke exposure.

Methods: Information on exposure to SHS and maternal smoking during pregnancy was collected on 3,318 participants at enrollment into the Southern California Children's Health Study. At study entry at average age of 10 years, residential near-roadway pollution exposure (NRP) was estimated based on a line source dispersion model accounting for traffic volume, proximity, and meteorology. Lifetime exposure to tobacco smoke was assessed by parent questionnaire. Associations with subsequent BMI growth trajectory based on annual measurements and attained BMI at 18 years of age were assessed using a multilevel modeling strategy.

Results: Maternal smoking during pregnancy was associated with estimated BMI growth over 8-year follow-up (0.72 kg/m² higher; 95% CI: 0.14, 1.31) and attained BMI (1.14 kg/m² higher; 95% CI: 0.66, 1.62). SHS exposure before enrollment was positively associated with BMI growth (0.81 kg/m² higher; 95% CI: 0.36, 1.27) and attained BMI (1.23 kg/m² higher; 95% CI: 0.86, 1.61). Growth and attained BMI increased with more smokers in the home. Compared with children without a history of SHS and NRP below the median, attained BMI was 0.80 kg/m² higher (95% CI: 0.27, 1.32) with exposure to high NRP without SHS; 0.85 kg/m² higher (95% CI: 0.43, 1.28) with low NRP and a history of SHS; and 2.15 kg/m² higher (95% CI: 1.52, 2.77) with high NRP and a history of SHS (interaction *p*-value 0.007). These results suggest a synergistic effect.

Conclusions: Our findings strengthen emerging evidence that exposure to tobacco smoke and NRP contribute to development of childhood obesity and suggest that combined exposures may have synergistic effects.

RELATED ARTICLES

FOCUS | The WASH Approach: Fighting Waterborne Diseases in Emergency Situations

Wendee Nicole | A6 (January 2015)

<http://dx.doi.org/10.1289/ehp.123-A6>

Emergency situations are prime settings for outbreaks of diseases spread by fecal–oral transmission. In times of scarcity, water tends to go first to drinking and cooking, while hygiene often gets short shrift. Having adequate water is not enough, however; health-protective behaviors are critically important for preventing the spread of waterborne diseases.



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BRIEF COMMUNICATION | Current Research and Opportunities to Address Environmental Asbestos Exposures

Danielle J. Carlin, Theodore C. Larson, Jean C. Pfau, Stephen H. Gavett, Arti Shukla, Aubrey Miller, and Ronald Hines | A194 (August 2015)
<http://dx.doi.org/10.1289/ehp.1409662>

Prenatal and Postnatal Exposure to Persistent Organic Pollutants and Infant Growth: A Pooled Analysis of Seven European Birth Cohorts

Nina Iszatt, Hein Stigum, Marc-André Verner, Richard A. White, Eva Govarts, Lubica Palkovicova Murinova, Greet Schoeters, Tomas Trnovec, Juliette Legler, Fabienne Pelé, Jérémie Botton, Cécile Chevrier, Jürgen Wittsiepe, Ulrich Ranft, Stéphanie Vandentorren, Monika Kasper-Sonnenberg, Claudia Klümper, Nynke Weisglas-Kuperus, Anuschka Polder, Merete Eggesbø, and OBELIX

123:730–736 (July 2015)

<http://dx.doi.org/10.1289/ehp.1308005>

Background: Infant exposure to persistent organic pollutants (POPs) may contribute to obesity. However, many studies so far have been small, focused on transplacental exposure, used an inappropriate measure to assess postnatal exposure through breastfeeding if any, or did not discern between prenatal and postnatal effects.

Objectives: We investigated prenatal and postnatal exposure to POPs and infant growth (a predictor of obesity).

Methods: We pooled data from seven European birth cohorts with biomarker concentrations of polychlorinated biphenyl 153 (PCB-153) ($n = 2,487$), and p,p' -dichlorodiphenyldichloroethylene (p,p' -DDE) ($n = 1,864$), estimating prenatal and postnatal POPs exposure using a validated pharmacokinetic model. Growth was change in weight-for-age z-score between birth and 24 months. Per compound, multilevel models were fitted with either POPs total exposure from conception to 24 months or prenatal or postnatal exposure.

Results: We found a significant increase in growth associated with p,p' -DDE, seemingly due to prenatal exposure (per interquartile increase in exposure, adjusted $\beta = 0.12$; 95% CI: 0.03, 0.22). Due to heterogeneity across cohorts, this estimate cannot be considered precise, but does indicate that an association with infant growth is present on average. In contrast, a significant decrease in growth was associated with postnatal PCB-153 exposure ($\beta = -0.10$; 95% CI: $-0.19, -0.01$).

Conclusion: To our knowledge, this is the largest study to date of POPs exposure and infant growth, and it contains state-of-the-art exposure modeling. Prenatal p,p' -DDE was associated with increased infant growth, and postnatal PCB-153 with decreased growth at European exposure levels.

ADVANCE PUBLICATION | Thyroid Antagonists (Perchlorate, Thiocyanate, and Nitrate) and Childhood Growth in a Longitudinal Study of U.S. Girls

Nancy A. Mervish, Ashley Pajak, Susan L. Teitelbaum, Susan M. Pinney, Gayle C. Windham, Lawrence H. Kushi, Frank M. Biro, Liza Valentin-Blasini, Benjamin C. Blount, and Mary S. Wolff, for the Breast Cancer and Environment Research Project (BCERP)

<http://dx.doi.org/10.1289/ehp.1409309>

ADVANCE PUBLICATION | Prenatal Phthalate Exposures and Childhood Fat Mass in a New York City Cohort

Jessie P. Buckley, Stephanie M. Engel, Michelle A. Mendez, David B. Richardson, Julie L. Daniels, Antonia M. Calafat, Mary S. Wolff, and Amy H. Herring

<http://dx.doi.org/10.1289/ehp.1509788>

DIABETES

Association between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis

Ikenna C. Eze, Lars G. Hemkens, Heiner C. Bucher, Barbara Hoffmann, Christian Schindler, Nino Künzli, Tamara Schikowski, and Nicole M. Probst-Hensch

123:381–389 (May 2015)

<http://dx.doi.org/10.1289/ehp.1307823>

Background: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated.

Objectives: We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM).

Methods: We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potential confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.

Results: We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM_{2.5} (particulate matter ≤ 2.5 μm in diameter) and 4 studies on NO₂ (nitrogen dioxide) showed increased risk of T2DM by 8–10% per 10- $\mu\text{g}/\text{m}^3$ increase in exposure [PM_{2.5}: 1.10 (95% CI: 1.02, 1.18); NO₂: 1.08 (95% CI: 1.00, 1.17)]. Associations were stronger in females. Sensitivity analyses showed similar results.

Conclusion: Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.

» NEWS | SCIENCE SELECTION

Air Pollution and Diabetes Risk: Assessing the Evidence to Date

Wendee Nicole | A134 (May 2015)

<http://dx.doi.org/10.1289/ehp.123-A134>

RELATED ARTICLES

FOCUS | Beyond Malnutrition: The Role of Sanitation in Stunted Growth

Charles W. Schmidt | A298 (November 2014)

<http://dx.doi.org/10.1289/ehp.122-A298>

Worldwide, stunted growth affects an estimated 165 million children under age 5. Reducing stunting is a global priority for international health organizations and donors, but it's clear that nutritional interventions alone won't get the job done. That's because stunting isn't just a nutritional problem; it's also an environmental one.



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FOCUS | Pollinator Power: Nutrition Security Benefits of an Ecosystem Service

Wendee Nicole | A210 (August 2015)

<http://dx.doi.org/10.1289/ehp.123-A210>

Scientists have only recently calculated the extent to which food supplies depend on pollinators. Now several new studies suggest that reduced populations of bees and other pollinators may adversely affect not only the marketplace but also the availability of essential nutrients in the human diet, potentially increasing malnutrition in areas already struggling with this issue.

HEAVY METALS (E.G., LEAD, MERCURY)

Blood Lead Concentration and Thyroid Function during Pregnancy: Results from the Yugoslavia Prospective Study of Environmental Lead Exposure

Linda G. Kahn, Xinhua Liu, Biljana Rajovic, Dusan Popovac, Sharon Oberfield, Joseph H. Graziano, and Pam Factor-Litvak

122:1134–1140 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307669>

Background: Although maternal hypothyroidism increases the risk of adverse neonatal and obstetric outcomes as well as lower IQ in children, the environmental determinants of maternal thyroid dysfunction have yet to be fully explored.

Objectives: We aimed to examine associations between mid-pregnancy blood lead (BPb) and concomitant measures of thyroid function among participants in the Yugoslavia Prospective Study of Environmental Lead Exposure.

Methods: As part of a population-based prospective study of two towns in Kosovo—one with high levels of environmental lead and one with low—women were recruited during the second trimester of pregnancy, at which time blood samples and questionnaire data were collected. We measured concentrations of BPb, free thyroxine (FT₄), thyroid-stimulating hormone (TSH), and thyroid peroxidase antibodies (TPOAb) in archived serum samples.

Results: Compared with women from the unexposed town, women from the exposed town had lower mean FT₄ (0.91 ± 0.17 vs. 1.03 ± 0.16 ng/dL), higher mean TPOAb (15.45 ± 33.08 vs. 5.12 ± 6.38 IU/mL), and higher mean BPb (20.00 ± 6.99 vs. 5.57 ± 2.01 µg/dL). No differences in TSH levels were found. After adjustment for potential confounders, for each natural log unit increase in BPb, FT₄ decreased by 0.074 ng/dL (95% CI: –0.10, –0.046 ng/dL), and the odds ratio for testing positive to TPOAb was 2.41 (95% CI: 1.53, 3.82). We found no association between BPb and TSH.

Conclusions: Prolonged lead exposure may contribute to maternal thyroid dysfunction by stimulating autoimmunity to the thyroid gland.

Association of Arsenic and Metals with Concentrations of 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D among Adolescents in Torreón, Mexico

Rachel D. Zamoiski, Eliseo Guallar, Gonzalo G. García-Vargas, Stephen J. Rothenberg, Carol Resnick, Marisela Rubio Andrade, Amy J. Steuerwald, Patrick J. Parsons, Virginia M. Weaver, Ana Navas-Acien, and Ellen K. Silbergeld

122:1233–1238 (November 2014)

<http://dx.doi.org/10.1289/ehp.1307861>

Background: Limited data suggest that lead (Pb), cadmium (Cd), and uranium (U) may disrupt vitamin D metabolism and inhibit production of 1,25-dihydroxyvitamin D [1,25(OH)₂D], the active vitamin D metabolite, from 25-hydroxyvitamin D [25(OH)D] in the kidney.

Objectives: We evaluated the association between blood lead (BPb) and urine arsenic (As), Cd, molybdenum (Mo), thallium (Tl), and U with markers of vitamin D metabolism [25(OH)D and 1,25(OH)₂D].

Methods: We conducted a cross-sectional study of 512 adolescents in Torreón, a town in Mexico with a Pb smelter near residential areas. BPb was measured using atomic absorption spectrometry. Urine As, Cd, Mo, Tl, and U were measured using inductively coupled plasma mass spectrometry. Serum 25(OH)D and 1,25(OH)₂D were measured using a chemiluminescent immunoassay and a radioimmunoassay, respectively. Multivariable linear models with vitamin D markers as the outcome were used to estimate associations of BPb and creatinine-corrected urine As and metal concentrations with serum vitamin D concentrations, controlling for age, sex, adiposity, smoking, socioeconomic status, and time outdoors.

Results: Serum 25(OH)D was positively associated with urine Mo and Tl [1.5 (95% CI: 0.4, 2.6) and 1.2 (95% CI: 0.3, 2.1) ng/mL higher with a doubling of exposure, respectively]. Serum 1,25(OH)₂D was positively associated with urine As and U [3.4 (95% CI: 0.9, 5.9) and 2.2 (95% CI: 0.7, 3.7) pg/mL higher, respectively], with little change in associations after additional adjustment for serum 25(OH)D. Pb and Cd were not associated with 25(OH)D or 1,25(OH)₂D concentrations.

Conclusions: Overall, our findings did not support a negative effect of As or metal exposures on serum 1,25(OH)₂D concentrations. Additional research is needed to confirm positive associations between serum 1,25(OH)₂D and urine U and As concentrations and to clarify potential underlying mechanisms.

Association of Arsenic with Adverse Pregnancy Outcomes/Infant Mortality: A Systematic Review and Meta-Analysis

Reginald Quansah, Frederick Ato Armah, David Kofi Essumang, Isaac Luginaah, Edith Clarke, Kissinger Marfoh, Samuel Jerry Cobbina, Edward Nketiah-Amponsah, Proscovia Bazanya Namujju, Samuel Obiri, and Mawuli Dzodzomenyo

123:412–421 (May 2015)

<http://dx.doi.org/10.1289/ehp.1307894>

Background: Exposure to arsenic is one of the major global health problems, affecting > 300 million people worldwide, but arsenic's effects on human reproduction are uncertain.

Objectives: We conducted a systematic review and meta-analysis to examine the association between arsenic and adverse pregnancy outcomes/infant mortality.

Methods: We searched PubMed and Ovid MEDLINE (from 1946 through July 2013) and EMBASE (from 1988 through July 2013) databases and the reference lists of reviews and relevant articles. Studies satisfying our *a priori* eligibility criteria were evaluated independently by two authors.

Results: Our systematic search yielded 888 articles; of these, 23 were included in the systematic review. Sixteen provided sufficient data for our quantitative analysis. Arsenic in groundwater (≥ 50 $\mu\text{g/L}$) was associated with increased risk of spontaneous abortion (6 studies: OR = 1.98; 95% CI: 1.27, 3.10), stillbirth (9 studies: OR = 1.77; 95% CI: 1.32, 2.36), moderate risk of neonatal mortality (5 studies: OR = 1.51; 95% CI: 1.28, 1.78), and infant mortality (7 studies: OR = 1.35; 95% CI: 1.12, 1.62). Exposure to environmental arsenic was associated with a significant reduction in birth weight (4 studies: $\beta = -53.2$ g; 95% CI: -94.9, -11.4). There was paucity of evidence for low-to-moderate arsenic dose.

Conclusions: Arsenic is associated with adverse pregnancy outcomes and infant mortality. The interpretation of the causal association is hampered by methodological challenges and limited number of studies on dose response. Exposure to arsenic continues to be a major global health issue, and we therefore advocate for high-quality prospective studies that include individual-level data to quantify the impact of arsenic on adverse pregnancy outcomes/infant mortality.

Estimated Exposure to Arsenic in Breastfed and Formula-Fed Infants in a United States Cohort

Courtney C. Carignan, Kathryn L. Cottingham, Brian P. Jackson, Shohreh F. Farzan, A. Jay Gandolfi, Tracy Punshon, Carol L. Folt, and Margaret R. Karagas

123:500–506 (May 2015)

<http://dx.doi.org/10.1289/ehp.1408789>

Background: Previous studies indicate that concentrations of arsenic in breast milk are relatively low even in areas with high drinking-water arsenic. However, it is uncertain whether breastfeeding leads to reduced infant exposure to arsenic in regions with lower arsenic concentrations.

Objective: We estimated the relative contributions of breast milk and formula to arsenic exposure during early infancy in a U.S. population.

Methods: We measured arsenic in home tap water ($n = 874$), urine from 6-week-old infants ($n = 72$), and breast milk from mothers ($n = 9$) enrolled in the New Hampshire Birth Cohort Study (NHBCS) using inductively coupled plasma mass spectrometry. Using data from a 3-day food diary, we compared urinary arsenic across infant feeding types and developed predictive exposure models to estimate daily arsenic intake from breast milk and formula.

Results: Urinary arsenic concentrations were generally low (median, 0.17 $\mu\text{g/L}$; maximum, 2.9 $\mu\text{g/L}$) but 7.5 times higher for infants fed exclusively with formula than for infants fed exclusively with breast milk ($\beta = 2.02$; 95% CI: 1.21, 2.83; $p < 0.0001$, adjusted for specific gravity). Similarly, the median estimated daily arsenic intake by NHBCS infants was 5.5 times higher for formula-fed infants (0.22 $\mu\text{g/kg/day}$) than for breastfed infants (0.04 $\mu\text{g/kg/day}$). Given median arsenic concentrations measured in NHBCS tap water and previously published for formula powder, formula powder was estimated to account for ~ 70% of median exposure among formula-fed NHBCS infants.

Conclusions: Our findings suggest that breastfed infants have lower arsenic exposure than formula-fed infants, and that both formula powder and drinking water can be sources of exposure for U.S. infants.

» NEWS | SCIENCE SELECTION

Arsenic Exposure in Infancy: Estimating the Contributions of Well Water and Human Milk

Charles W. Schmidt | A137 (May 2015)

<http://dx.doi.org/10.1289/ehp.123-A137>

Arsenic Exposure and Prevalence of the Varicella Zoster Virus in the United States: NHANES (2003–2004 and 2009–2010)

Andres Cardenas, Ellen Smit, E. Andres Houseman, Nancy I. Kerkvliet, Jeffrey W. Bethel, and Molly L. Kile

123:590–596 (June 2015)
<http://dx.doi.org/10.1289/ehp.1408731>

Background: Arsenic is an immunotoxicant. Clinical reports observe the reactivation of varicella zoster virus (VZV) in people who have recovered from arsenic poisoning and in patients with acute promyelocytic leukemia that have been treated with arsenic trioxide.

Objective: We evaluated the association between arsenic and the seroprevalence of VZV IgG antibody in a representative sample of the U.S. population.

Methods: We analyzed data from 3,348 participants of the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and 2009–2010 pooled survey cycles. Participants were eligible if they were 6–49 years of age with information on both VZV IgG and urinary arsenic concentrations. We used two measures of total urinary arsenic (TUA): TUA1 was defined as the sum of arsenite, arsenate, monomethylarsonic acid, and dimethylarsinic acid, and TUA2 was defined as total urinary arsenic minus arsenobetaine and arsenocholine.

Results: The overall weighted seronegative prevalence of VZV was 2.2% for the pooled NHANES sample. The geometric means of TUA1 and TUA2 were 6.57 µg/L and 5.64 µg/L, respectively. After adjusting for age, sex, race, income, creatinine, and survey cycle, odds ratios for a negative VZV IgG result in association with 1-unit increases in natural log-transformed (ln)-TUA1 and ln-TUA2 were 1.87 (95% CI: 1.03, 3.44) and 1.40 (95% CI: 1.0, 1.97), respectively.

Conclusions: In this cross-sectional analysis, urinary arsenic was inversely associated with VZV IgG seroprevalence in the U.S. population. This finding is in accordance with clinical observations of zoster virus reactivation from high doses of arsenic. Additional studies are needed to confirm the association and evaluate causal mechanisms.

Blood Pressure, Left Ventricular Geometry, and Systolic Function in Children Exposed to Inorganic Arsenic

Citlalli Osorio-Yáñez, Julio C. Ayllon-Vergara, Laura Arreola-Mendoza, Guadalupe Aguilar-Madrid, Erika Hernández-Castellanos, Luz C. Sánchez-Peña, and Luz M. Del Razo

123:629–635 (June 2015)
<http://dx.doi.org/10.1289/ehp.1307327>

Background: Inorganic arsenic (iAs) is a ubiquitous element present in the groundwater worldwide. Cardiovascular effects related to iAs exposure have been studied extensively in adult populations. Few epidemiological studies have been focused on iAs exposure-related cardiovascular disease in children.

Objective: In this study we investigated the association between iAs exposure, blood pressure (BP), and functional and anatomical echocardiographic parameters in children.

Methods: A cross-sectional study of 161 children between 3 and 8 years was conducted in Central Mexico. The total concentration of arsenic (As) species in urine (U-tAs) was determined by hydride generation–cryotrapping–atomic absorption spectrometry and lifetime iAs exposure was estimated by multiplying As concentrations measured in drinking water by the duration of water consumption in years (LAsE). BP was measured by standard protocols, and M-mode echocardiographic parameters were determined by ultrasonography.

Results: U-tAs concentration and LAsE were significantly associated with diastolic (DBP) and systolic blood pressure (SBP) in multivariable linear regression models: DBP and SBP were 0.013 (95% CI: 0.002, 0.024) and 0.021 (95% CI: 0.004, 0.037) mmHg higher in association with each 1-ng/mL increase in U-tAs ($p < 0.025$), respectively. Left ventricular mass (LVM) was significantly associated with LAsE [5.5 g higher (95% CI: 0.65, 10.26) in children with LAsE > 620 compared with < 382 µg/L-year; $p = 0.03$] in an adjusted multivariable model. The systolic function parameters left ventricular ejection fraction (EF) and shortening fraction were 3.67% (95% CI: –7.14, –0.20) and 3.41% (95% CI: –6.44, –0.37) lower, respectively, in children with U-tAs > 70 ng/mL compared with < 35 ng/mL.

Conclusion: Early-life exposure to iAs was significantly associated with higher BP and LVM and with lower EF in our study population of Mexican children.

Mercury Exposure and Antinuclear Antibodies among Females of Reproductive Age in the United States: NHANES

Emily C. Somers, Martha A. Ganser, Jeffrey S. Warren, Niladri Basu, Lu Wang, Suzanna M. Zick, and Sung Kyun Park

123:792–798 (August 2015)

<http://dx.doi.org/10.1289/ehp.1408751>

Background: Immune dysregulation associated with mercury has been suggested, although data in the general population are lacking. Chronic exposure to low levels of methylmercury (organic) and inorganic mercury is common, such as through fish consumption and dental amalgams.

Objective: We examined associations between mercury biomarkers and antinuclear antibody (ANA) positivity and titer strength.

Methods: Among females 16–49 years of age ($n = 1,352$) from the National Health and Nutrition Examination Survey (NHANES) 1999–2004, we examined cross-sectional associations between mercury and ANAs (indirect immunofluorescence; cutoff $\geq 1:80$). Three biomarkers of mercury exposure were used: hair (available 1999–2000) and total blood (1999–2004) predominantly represented methylmercury, and urine (1999–2002) represented inorganic mercury. Survey statistics were used. Multivariable modeling adjusted for several covariates, including age and omega-3 fatty acids.

Results: Sixteen percent of females were ANA positive; 96% of ANA positives had a nuclear speckled staining pattern. Geometric mean (geometric SD) mercury concentrations were 0.22 (0.03) ppm in hair, 0.92 (0.05) $\mu\text{g/L}$ blood, and 0.62 (0.04) $\mu\text{g/L}$ urine. Hair and blood, but not urinary, mercury were associated with ANA positivity (sample sizes 452, 1,352, and 804, respectively), after adjusting for confounders: for hair, odds ratio (OR) = 4.10 (95% CI: 1.66, 10.13); for blood, OR = 2.32 (95% CI: 1.07, 5.03) comparing highest versus lowest quantiles. Magnitudes of association were strongest for high-titer ($\geq 1:1,280$) ANA: hair, OR = 11.41 (95% CI: 1.60, 81.23); blood, OR = 5.93 (95% CI: 1.57, 22.47).

Conclusions: Methylmercury, at low levels generally considered safe, was associated with subclinical autoimmunity among reproductive-age females. Autoantibodies may predate clinical disease by years; thus, methylmercury exposure may be relevant to future autoimmune disease risk.

ADVANCE PUBLICATION | Evaluation of an Elementary School–based Educational Intervention for Reducing Arsenic Exposure in Bangladesh

Khalid Khan, Ershad Ahmed, Pam Factor-Litvak, Xinhua Liu, Abu B. Siddique, Gail A. Wasserman, Vesna Slavkovich, Diane Levy, Jacob L. Mey, Alexander van Geen, and Joseph H. Graziano

<http://dx.doi.org/10.1289/ehp.1409462>

ADVANCE PUBLICATION | A Case–Control Study of Prenatal Thallium Exposure and Low Birth Weight in China

Wei Xia, Xiaofu Du, Bin Zhang, Yuanyuan Li, Bryan A. Bassig, Aifen Zhou, Youjie Wang, Chao Xiong, Zhengkuan Li, Yuanxiang Yao, Jie Hu, Yanqiu Zhou, Qi Wang, Juan Liu, Weiyan Xue, Yue Ma, Xinyun Pan, Yang Peng, Tongzhang Zheng, and Shunqing Xu

<http://dx.doi.org/10.1289/ehp.1409202>

ADVANCE PUBLICATION | Confusion about Cadmium Risks: The Unrecognized Limitations of an Extrapolated Paradigm

Alfred Bernard

<http://dx.doi.org/10.1289/ehp.1509691>

ADVANCE PUBLICATION | Use of a Cumulative Exposure Index to Estimate the Impact of Tap-Water Lead Concentration on Blood Lead Levels in 1- to 5-Year-Old Children (Montreal, Canada)

Gerard Ngueta, Belkacem Abdous, Robert Tardif, Julie St-Laurent, and Patrick Levallois

<http://dx.doi.org/10.1289/ehp.1409144>

PESTICIDES AND OTHER CHEMICALS/ COMPOUNDS (E.G., BPA, PCBs, PBDEs, PFCs, PHTHALATES, ENDOCRINE DISRUPTORS)

Early-Life Bisphenol A Exposure and Child Body Mass Index: A Prospective Cohort Study

Joseph M. Braun, Bruce P. Lanphear, Antonia M. Calafat, Sirad Deria, Jane Khoury, Channele J. Howe, and Scott A. Venners

122:1239–1245 (November 2014)
<http://dx.doi.org/10.1289/ehp.1408258>

Background: Early-life exposure to bisphenol A (BPA) may increase childhood obesity risk, but few prospective epidemiological studies have investigated this relationship.

Objective: We sought to determine whether early-life exposure to BPA was associated with increased body mass index (BMI) at 2–5 years of age in 297 mother–child pairs from Cincinnati, Ohio (HOME Study).

Methods: Urinary BPA concentrations were measured in samples collected from pregnant women during the second and third trimesters and their children at 1 and 2 years of age. BMI z-scores were calculated from weight/height measures conducted annually from 2 through 5 years of age. We used linear mixed models to estimate BMI differences or trajectories with increasing creatinine-normalized BPA concentrations.

Results: After confounder adjustment, each 10-fold increase in prenatal ($\beta = -0.1$; 95% CI: $-0.5, 0.3$) or early-childhood ($\beta = -0.2$; 95% CI: $-0.6, 0.1$) BPA concentrations was associated with a modest and nonsignificant reduction in child BMI. These inverse associations were suggestively stronger in girls than in boys [prenatal effect measure modification (EMM) p -value = 0.30, early-childhood EMM p -value = 0.05], but sex-specific associations were imprecise. Children in the highest early-childhood BPA tercile had lower BMI at 2 years (difference = -0.3 ; 95% CI: $-0.6, 0.0$) and larger increases in their BMI slope from 2 through 5 years (BMI increase per year = 0.12; 95% CI: 0.07, 0.18) than children in the lowest tercile (BMI increase per year = 0.07; 95% CI: 0.01, 0.13). All associations were attenuated without creatinine normalization.

Conclusions: Prenatal and early-childhood BPA exposures were not associated with increased BMI at 2–5 years of age, but higher early-childhood BPA exposures were associated with accelerated growth during this period.

Aerial Application of Mancozeb and Urinary Ethylene Thiourea (ETU) Concentrations among Pregnant Women in Costa Rica: The Infants' Environmental Health Study (ISA)

Berna van Wendel de Joode, Ana María Mora, Leonel Córdoba, Juan Camilo Cano, Rosario Quesada, Moosa Faniband, Catharina Wesseling, Clemens Ruepert, Mattias Öberg, Brenda Eskenazi, Donna Mergler, and Christian H. Lindh

122:1321–1328 (December 2014)
<http://dx.doi.org/10.1289/ehp.1307679>

Background: Mancozeb and its main metabolite ethylene thiourea (ETU) may alter thyroid function; thyroid hormones are essential for fetal brain development. In Costa Rica, mancozeb is aerially sprayed at large-scale banana plantations on a weekly basis.

Objectives: Our goals were to evaluate urinary ETU concentrations in pregnant women living near large-scale banana plantations, compare their estimated daily intake (EDI) with established reference doses (RfDs), and identify factors that predict their urinary ETU concentrations.

Methods: We enrolled 451 pregnant women from Matina County, Costa Rica, which has large-scale banana production. We visited 445 women up to three times during pregnancy to obtain urine samples ($n = 872$) and information on factors that possibly influence exposure. We determined urinary ETU concentrations using liquid chromatography mass spectrometry.

Results: Pregnant women's median urinary ETU concentrations were more than five times higher than those reported for other general populations. Seventy-two percent of the women had EDIs above the RfD. Women who lived closest (1st quartile, < 48 m) to banana plantations on average had a 45% (95% CI: 23, 72%) higher urinary ETU compared with women who lived farthest away (4th quartile, ≥ 565 m). Compared with the other women, ETU was also higher in women who washed agricultural work clothes on the day before sampling (11%; 95% CI: 4.9, 17%), women who worked in agriculture during pregnancy (19%; 95% CI: 9.3, 29%), and immigrant women (6.2%; 95% CI: 1.0, 13%).

Conclusions: The pregnant women's urinary ETU concentrations are of concern, and the principal source of exposure is likely to be aerial spraying of mancozeb. The factors predicting ETU provide insight into possibilities for exposure reduction.

» NEWS | SCIENCE SELECTION

Assessing the Impact of Aerial Spraying: Mancozeb Exposures among Pregnant Women Living near Banana Plantations

Carol Potera | A337 (December 2014)
<http://dx.doi.org/10.1289/ehp.122-A337>

Evaluating Health Risks from Inhaled Polychlorinated Biphenyls: Research Needs for Addressing Uncertainty

Geniece M. Lehmann, Krista Christensen, Mark Maddaloni, and Linda J. Phillips

123:109–113 (February 2015)

<http://dx.doi.org/10.1289/ehp.1408564>

Background: Indoor air concentrations of polychlorinated biphenyls (PCBs) in some buildings are one or more orders of magnitude higher than background levels. In response to this, efforts have been made to assess the potential health risk posed by inhaled PCBs. These efforts are hindered by uncertainties related to the characterization and assessment of source, exposure, and exposure-response.

Objectives: We briefly describe some common sources of PCBs in indoor air and estimate the contribution of inhalation exposure to total PCB exposure for select age groups. Next, we identify critical areas of research needed to improve assessment of exposure and exposure response for inhaled PCBs.

Discussion: Although the manufacture of PCBs was banned in the United States in 1979, many buildings constructed before then still contain potential sources of indoor air PCB contamination. In some indoor settings and for some age groups, inhalation may contribute more to total PCB exposure than any other route of exposure. PCB exposure has been associated with human health effects, but data specific to the inhalation route are scarce. To support exposure–response assessment, it is critical that future investigations of the health impacts of PCB inhalation carefully consider certain aspects of study design, including characterization of the PCB mixture present.

Conclusions: In certain contexts, inhalation exposure to PCBs may contribute more to total PCB exposure than previously assumed. New epidemiological and toxicological studies addressing the potential health impacts of inhaled PCBs may be useful for quantifying exposure–response relationships and evaluating risks.

RELATED ARTICLES

SPHERES OF INFLUENCE | In Search of “Just Right”: The Challenge of Regulating Arsenic in Rice

Charles W. Schmidt | A16 (January 2015)
<http://dx.doi.org/10.1289/ehp.123-A16>

Many countries regulate arsenic in municipal water. Now research and regulatory concerns are broadening to include arsenic in the diet, especially in rice, but settling on an appropriate limit for arsenic in rice is proving difficult.



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FOCUS | Hand-Me-Down Hazard: Flame Retardants in Discarded Foam Products

Kellyn S. Betts | A56 (March 2015)
<http://dx.doi.org/10.1289/ehp.123-A56>

Furniture industry experts expect flame-retardant-free furnishings to become increasingly popular with consumers who can afford them, and people who purchase these items may reduce their exposures to certain flame retardants. But what happens to older furniture that enters the waste stream?

Exposure to Free and Conjugated Forms of Bisphenol A and Triclosan among Pregnant Women in the MIREC Cohort

Tye E. Arbuckle, Leonora Marro, Karelyn Davis, Mandy Fisher, Pierre Ayotte, Patrick Bélanger, Pierre Dumas, Alain LeBlanc, René Bérubé, Éric Gaudreau, Gilles Provencher, Elaine M. Faustman, Eric Vigoren, Adrienne S. Ettinger, Michael Dellarco, Susan MacPherson, and William D. Fraser

123:277–284 (April 2015)

<http://dx.doi.org/10.1289/ehp.1408187>

Background: Bisphenol A (BPA) and triclosan (TCS) are two nonpersistent chemicals that have been frequently measured in spot urine samples from the general population but less so in pregnant women; however, data are limited on the free (bioactive) and conjugated forms of these phenols.

Objectives: The Maternal-Infant Research on Environmental Chemicals (MIREC) Study addressed these data gaps by utilizing stored maternal urine samples from a large multicenter cohort study of Canadian pregnant women.

Methods: Concentrations of free and conjugated forms of BPA and TCS were measured in about 1,890 first-trimester urine samples by ultra performance liquid chromatography–tandem mass spectrometry using isotope dilution.

Results: The glucuronides of BPA and TCS were the predominant forms of these chemicals measured (detected in 95% and 99% of samples, respectively), whereas the free forms were detected in 43% and 80% of samples, respectively. The geometric mean urinary concentrations for glucuronides of BPA and TCS were 0.80 µg/L (95% CI: 0.75, 0.85) and 12.30 µg/L (95% CI: 11.08, 13.65), respectively. Significant predictors of BPA included maternal age < 25 vs. ≥ 35 years, current smoking, low vs. high household income, and low vs. high education. For TCS, urinary concentrations were significantly higher in women ≥ 25 years of age, never vs. current smokers, and women with high household income and high education.

Conclusions: The results from this study represent the largest national-level data on urinary concentrations of free and conjugated forms of BPA and TCS in pregnant women and suggest that maternal characteristics predicting elevated urinary concentrations of these phenols largely act in opposite directions.

In Utero and Childhood Polybrominated Diphenyl Ether Exposures and Body Mass at Age 7 Years: The CHAMACOS Study

Ayca Erkin-Cakmak, Kim G. Harley, Jonathan Chevrier, Asa Bradman, Katherine Kogut, Karen Huen, and Brenda Eskenazi

123:636–642 (June 2015)

<http://dx.doi.org/10.1289/ehp.1408417>

Background: Polybrominated diphenyl ethers (PBDEs) are lipophilic flame retardants that bioaccumulate in humans. Child serum PBDE concentrations in California are among the highest worldwide. PBDEs may be associated with obesity by disrupting endocrine systems.

Objective: In this study, we examined whether pre- and postnatal exposure to the components of pentaBDE mixture was associated with childhood obesity in a population of Latino children participating in a longitudinal birth cohort study in the Salinas Valley, California.

Methods: We measured PBDEs in serum collected from 224 mothers during pregnancy and their children at 7 years of age, and examined associations with body mass index (BMI) at age 7 years.

Results: Maternal PBDE serum levels during pregnancy were associated with higher BMI z-scores in boys (BMI z-score $\beta_{\text{adjusted}} = 0.26$; 95% CI: –0.19, 0.72) but lower scores in girls (BMI z-score $\beta_{\text{adjusted}} = -0.41$; 95% CI: –0.87, –0.05) at 7 years of age ($p_{\text{interaction}} = 0.04$). In addition, child's serum BDE-153 concentration (\log_{10}), but not other pentaBDE congeners, demonstrated inverse associations with BMI at age 7 years (BMI z-score $\beta_{\text{adjusted}} = -1.15$; 95% CI: –1.53, –0.77), but there was no interaction by sex.

Conclusions: We estimated sex-specific associations with maternal PBDE levels during pregnancy and BMI at 7 years of age, finding positive associations in boys and negative associations in girls. Children's serum BDE-153 concentrations were inversely associated with BMI at 7 years with no difference by sex. Future studies should examine the longitudinal trends in obesity with PBDE exposure and changes in hormonal environment as children transition through puberty, as well as evaluate the potential for reverse causality.

Measurement of Total and Free Urinary Phenol and Paraben Concentrations over the Course of Pregnancy: Assessing Reliability and Contamination of Specimens in the Norwegian Mother and Child Cohort Study

Virginia T. Guidry, Matthew P. Longnecker, Heidi Aase, Merete Eggesbø, Pål Zeiner, Ted Reichborn-Kjennerud, Gun P. Knudsen, Randi J. Bertelsen, Xiaoyun Ye, Antonia M. Calafat, and Stephanie M. Engel

123:705–711 (July 2015)

<http://dx.doi.org/10.1289/ehp.1408325>

Background: Exposures to environmental phenols and parabens may be harmful, especially *in utero*. Prior studies have demonstrated high within-person variability of urinary concentrations across pregnancy.

Objectives: We sought to measure phenol and paraben biomarker concentrations for the Norwegian Mother and Child Cohort (MoBa) study, assess within-person variability, and investigate any possible external phenol or paraben contamination of specimens.

Methods: We collected three spot urine samples at approximately 17, 23, and 29 weeks gestation in a hospital setting and added a preservative containing ethyl paraben. We measured urinary concentrations and within-person variability for phenols and parabens in a MoBa sample ($n = 45$), including a subgroup of 15 participants previously randomly selected for a bisphenol A (BPA) exposure study who had unusually high total BPA concentrations. Additionally, we compared reliability results for total, conjugated, and free concentrations of phenolic compounds.

Results: We detected total and free BPA, butyl paraben, propyl paraben, and methyl paraben in 100% of samples, total benzophenone-3 in 95% of samples, and infrequently detected free benzophenone-3 and total and free 2,4-dichlorophenol and 2,5-dichlorophenol. Intraclass correlation coefficients (ICCs) for total, conjugated, and free concentrations ranged from relatively low for BPA to moderate for propyl paraben. ICCs were generally similar overall and by subgroup.

Conclusions: Using conjugated concentrations improved reliability estimates only for BPA. Measuring total and free concentrations, an approach that may be useful for future studies, allowed us to identify likely BPA and butyl paraben contamination of archived MoBa urine specimens.

Anthropometry in 5- to 9-Year-Old Greenlandic and Ukrainian Children in Relation to Prenatal Exposure to Perfluorinated Alkyl Substances

Birgit Bjerre Høyer, Cecilia Høst Ramlau-Hansen, Martine Vrijheid, Damaskini Valvi, Henning Sloth Pedersen, Valentyna Zvezdai, Bo A.G. Jönsson, Christian H. Lindh, Jens Peter Bonde, and Gunnar Toft

123:841–846 (August 2015)

<http://dx.doi.org/10.1289/ehp.1408881>

Background: In some animal studies, perfluorinated alkyl substances are suggested to induce weight gain. Human epidemiological studies investigating these associations are sparse.

Objective: We examined pregnancy serum concentrations of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) and the prevalence of offspring overweight (> 1 SD) and waist-to-height ratio (WHtR) > 0.5 at 5–9 years of age.

Methods: Sera from 1,022 pregnant women enrolled in the INUENDO cohort (2002–2004) from Greenland and Kharkiv (Ukraine) were analyzed for PFOA and PFOS using liquid chromatography–tandem mass spectrometry. Relative risks (RR) of being overweight and having WHtR > 0.5 in relation to continuous and categorized (tertiles) PFOA and PFOS were calculated at follow-up (2010–2012) using generalized linear models.

Results: Pooled PFOA median (range) was 1.3 (0.2–5.1) and PFOS median (range) was 10.8 (0.8–73.0) ng/mL. For each natural logarithm-unit (ln-unit) increase of pregnancy PFOA, the adjusted RR of offspring overweight was 1.11 [95% confidence interval (CI): 0.82, 1.53] in Greenlandic children. In Ukrainian children, the adjusted RR of offspring overweight was 1.02 (95% CI: 0.72, 1.44) for each ln-unit increase of pregnancy PFOA. Prenatal exposure to PFOS was not associated with overweight in country-specific or pooled analysis. The adjusted RR of having WHtR > 0.5 for each ln-unit increase of prenatal exposure to PFOA was 1.30 (95% CI: 0.97, 1.74) in the pooled analysis. For 1–ln-unit increase of prenatal exposure to PFOS, the adjusted RR of having a WHtR > 0.5 was 1.38 (95% CI: 1.05, 1.82) in the pooled analysis.

Conclusions: The results indicate that prenatal PFOA and PFOS exposures may be associated with child waist-to-height ratio > 0.5 . Prenatal PFOA and PFOS exposures were not associated with overweight.

ADVANCE PUBLICATION | Associations of Perfluoroalkyl Substances (PFASs) with Lower Birth Weight: An Evaluation of Potential Confounding by Glomerular Filtration Rate Using a Physiologically Based Pharmacokinetic Model (PBPK)

Marc-André Verner, Anne E. Loccisano, Nils-Halvdan Morken, Miyoung Yoon, Huali Wu, Robin McDougall, Mildred Maisonet, Michele Marcus, Reiko Kishi, Chihiro Miyashita, Mei-Huei Chen, Wu-Shiun Hsieh, Melvin E. Andersen, Harvey J. Clewell III, and Matthew P. Longnecker

<http://dx.doi.org/10.1289/ehp.1408837>

ADVANCE PUBLICATION | Prepubertal Serum Concentrations of Organochlorine Pesticides and Age at Sexual Maturity in Russian Boys

Thuy Lam, Paige L. Williams, Mary M. Lee, Susan A. Korrick, Linda S. Birnbaum, Jane S. Burns, Oleg Sergeyev, Boris Revich, Larisa M. Altshul, Donald G. Patterson Jr., and Russ Hauser

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<http://dx.doi.org/10.1289/ehp.1408907>

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Jessica LaRocca, Alexandra M. Binder, Thomas F. McElrath, and Karin B. Michels

<http://dx.doi.org/10.1289/ehp.1408409>

ADVANCE PUBLICATION | Prenatal Phthalate, Perfluoroalkyl Acid, and Organochlorine Exposures and Term Birth Weight in Three Birth Cohorts: Multi-Pollutant Models Based on Elastic Net Regression

Virissa Lenters, Lützen Portengen, Anna Rignell-Hydbom, Bo A.G. Jönsson, Christian H. Lindh, Aldert H. Piersma, Gunnar Toft, Jens Peter Bonde, Dick Heederik, Lars Rylander, and Roel Vermeulen

<http://dx.doi.org/10.1289/ehp.1408933>

ADVANCE PUBLICATION | Birth Weight, Ethnicity, and Exposure to Trihalomethanes and Haloacetic Acids in Drinking Water during Pregnancy in the Born in Bradford Cohort

Rachel B. Smith, Susan C. Edwards, Nicky Best, John Wright, Mark J. Nieuwenhuijsen, and Mireille B. Toledano

<http://dx.doi.org/10.1289/ehp.1409480>

AIR POLLUTION: PARTICULATE MATTER, SMOKE, INDOOR AIR

Sources of Fine Particulate Matter and Risk of Preterm Birth in Connecticut, 2000–2006: A Longitudinal Study

Gavin Pereira, Michelle L. Bell, Hyung Joo Lee, Petros Koutrakis, and Kathleen Belanger

122:1117–1122 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307741>

Background: Previous studies have examined fine particulate matter ($\leq 2.5 \mu\text{m}$; $\text{PM}_{2.5}$) and preterm birth, but there is a dearth of longitudinal studies on this topic and a paucity of studies that have investigated specific sources of this exposure.

Objectives: Our aim was to assess whether anthropogenic sources are associated with risk of preterm birth, comparing successive pregnancies to the same woman.

Methods: Birth certificates were used to select women who had vaginal singleton live births at least twice in Connecticut during 2000–2006 ($n = 23,123$ women, $n = 48,208$ births). We procured 4,085 daily samples of $\text{PM}_{2.5}$ on Teflon filters from the Connecticut Department of Environmental Protection for six cities in Connecticut. Filters were analyzed for chemical composition, and Positive Matrix Factorization was used to determine contributions of $\text{PM}_{2.5}$ sources. Risk estimates were calculated with conditional logistic regression, matching pregnancies to the same women.

Results: Odds ratios of preterm birth per interquartile range increase in whole pregnancy exposure to dust, motor vehicle emissions, oil combustion, and regional sulfur $\text{PM}_{2.5}$ sources were 1.01 (95% CI: 0.93, 1.09), 1.01 (95% CI: 0.92, 1.10), 1.00 (95% CI: 0.89, 1.12), and 1.09 (95% CI: 0.97, 1.22), respectively.

Conclusion: This was the first study of $\text{PM}_{2.5}$ sources and preterm birth, and the first matched analysis, that better addresses individual-level confounding potentially inherent in all past studies. There was insufficient evidence to suggest that sources were statistically significantly associated with preterm birth. However, elevated central estimates and previously observed associations with mass concentration motivate the need for further research. Future studies would benefit from high source exposure settings and longitudinal study designs, such as that adopted in this study.

RELATED ARTICLES

FOCUS | More than Cosmetic Changes: Taking Stock of Personal Care Product Safety

Rebecca Kessler | A120 (May 2015)

<http://dx.doi.org/10.1289/ehp.123-A120>

In recent years, under mounting pressure from advocacy groups, a number of major manufacturers and retailers have begun eliminating controversial ingredients from the personal care products they produce and sell. Companies are investing considerable resources to reformulate their products, even as they universally defend the questioned ingredients.



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SPHERES OF INFLUENCE | Chemical Footprinting: Identifying Hidden Liabilities in Manufacturing Consumer Products

Lindsey Konkel | A130 (May 2015)

<http://dx.doi.org/10.1289/ehp.123-A130>

Corporate chemicals management policies have traditionally revolved around making sure certain chemicals aren't found in products over a mandated threshold. Manufacturers are now going a step farther, using "chemical footprinting" to identify and manage hidden chemical liabilities in products and supply chains.

EDITORIAL | Alternatives to PFASs: Perspectives on the Science

Linda S. Birnbaum and Philippe Grandjean | A104 (May 2015)

<http://dx.doi.org/10.1289/ehp.1509944>

BRIEF COMMUNICATION | The Madrid Statement on Poly- and Perfluoroalkyl Substances (PFASs)

Arlene Blum, Simona A. Balan, Martin Scheringer, Xenia Trier, Gretta Goldenman, Ian T. Cousins, Miriam Diamond, Tony Fletcher, Christopher Higgins, Avery E. Lindeman, Graham Peaslee, Pim de Voogt, Zhanyun Wang, and Roland Weber | A107 (May 2015)

<http://dx.doi.org/10.1289/ehp.1509934>

BRIEF COMMUNICATION | Fluorotechnology Is Critical to Modern Life: The FluoroCouncil Counterpoint to the Madrid Statement

Jessica S. Bowman | A112 (May 2015)

<http://dx.doi.org/10.1289/ehp.1509910>

Evaluating Potential Response-Modifying Factors for Associations between Ozone and Health Outcomes: A Weight-of-Evidence Approach

Lisa C. Vinikoor-Imler, Elizabeth O. Owens, Jennifer L. Nichols, Mary Ross, James S. Brown, and Jason D. Sacks

122:1166–1176 (November 2014)
<http://dx.doi.org/10.1289/ehp.1307541>

Background: Epidemiologic and experimental studies have reported a variety of health effects in response to ozone (O₃) exposure, and some have indicated that certain populations may be at increased or decreased risk of O₃-related health effects.

Objectives: We sought to identify potential response-modifying factors to determine whether specific groups of the population or life stages are at increased or decreased risk of O₃-related health effects using a weight-of-evidence approach.

Methods: Epidemiologic, experimental, and exposure science studies of potential factors that may modify the relationship between O₃ and health effects were identified in U.S. Environmental Protection Agency's 2013 *Integrated Science Assessment for Ozone and Related Photochemical Oxidants*. Scientific evidence from studies that examined factors that may influence risk were integrated across disciplines to evaluate consistency, coherence, and biological plausibility of effects. The factors identified were then classified using a weight-of-evidence approach to conclude whether a specific factor modified the response of a population or life stage, resulting in an increased or decreased risk of O₃-related health effects.

Discussion: We found “adequate” evidence that populations with certain genotypes, preexisting asthma, or reduced intake of certain nutrients, as well as different life stages or outdoor workers, are at increased risk of O₃-related health effects. In addition, we identified other factors (i.e., sex, socioeconomic status, and obesity) for which there was “suggestive” evidence that they may increase the risk of O₃-related health effects.

Conclusions: Using a weight-of-evidence approach, we identified a diverse group of factors that should be considered when characterizing the overall risk of health effects associated with exposures to ambient O₃.

Prenatal Air Pollution Exposure and Newborn Blood Pressure

Lenie van Rossem, Sheryl L. Rifas-Shiman, Steven J. Melly, Itai Kloog, Heike Luttmann-Gibson, Antonella Zanobetti, Brent A. Coull, Joel D. Schwartz, Murray A. Mittleman, Emily Oken, Matthew W. Gillman, Petros Koutrakis, and Diane R. Gold

123:353–359 (April 2015)
<http://dx.doi.org/10.1289/ehp.1307419>

Background: Air pollution exposure has been associated with increased blood pressure in adults.

Objective: We examined associations of antenatal exposure to ambient air pollution with newborn systolic blood pressure (SBP).

Methods: We studied 1,131 mother–infant pairs in a Boston, Massachusetts, area pre-birth cohort. We calculated average exposures by trimester and during the 2 to 90 days before birth for temporally resolved fine particulate matter ($\leq 2.5 \mu\text{m}$; PM_{2.5}), black carbon (BC), nitrogen oxides, nitrogen dioxide, ozone (O₃), and carbon monoxide measured at stationary monitoring sites, and for spatiotemporally resolved estimates of PM_{2.5} and BC at the residence level. We measured SBP at a mean age of 30 ± 18 hr with an automated device. We used mixed-effects models to examine associations between air pollutant exposures and SBP, taking into account measurement circumstances; child's birth weight; mother's age, race/ethnicity, socioeconomic position, and third-trimester BP; and time trend. Estimates represent differences in SBP associated with an interquartile range (IQR) increase in each pollutant.

Results: Higher mean PM_{2.5} and BC exposures during the third trimester were associated with higher SBP (e.g., 1.0 mmHg; 95% CI: 0.1, 1.8 for a 0.32- $\mu\text{g}/\text{m}^3$ increase in mean 90-day residential BC). In contrast, O₃ was negatively associated with SBP (e.g., –2.3 mmHg; 95% CI: –4.4, –0.2 for a 13.5-ppb increase during the 90 days before birth).

Conclusions: Exposures to PM_{2.5} and BC in late pregnancy were positively associated with newborn SBP, whereas O₃ was negatively associated with SBP. Longitudinal follow-up will enable us to assess the implications of these findings for health during later childhood and adulthood.

» NEWS | SCIENCE SELECTION

Air Pollution and Neonatal Blood Pressure: Examining Earlier Exposures

Wendee Nicole | A94 (April 2015)
<http://dx.doi.org/10.1289/ehp.123-A94>

Blood Pressure and Same-Day Exposure to Air Pollution at School: Associations with Nano-Sized to Coarse PM in Children

Nicky Pieters, Gudrun Koppen, Martine Van Poppel, Sofie De Prins, Bianca Cox, Evi Dons, Vera Nelen, Luc Int Panis, Michelle Plusquin, Greet Schoeters, and Tim S. Nawrot

123:737–742 (July 2015)

<http://dx.doi.org/10.1289/ehp.1408121>

Background: Ultrafine particles (UFP) may contribute to the cardiovascular effects of particulate air pollution, partly because of their relatively efficient alveolar deposition.

Objective: In this study, we assessed associations between blood pressure and short-term exposure to air pollution in a population of schoolchildren.

Methods: In 130 children (6–12 years of age), blood pressure was determined during two periods (spring and fall 2011). We used mixed models to study the association between blood pressure and ambient concentrations of particulate matter and ultrafine particles measured in the schools' playground.

Results: Independent of sex, age, height, and weight of the child, parental education, neighborhood socioeconomic status, fish consumption, heart rate, school, day of the week, season, wind speed, relative humidity, and temperature on the morning of examination, an interquartile range (860 particles/cm³) increase in nano-sized UFP fraction (20–30 nm) was associated with a 6.35 mmHg (95% CI: 1.56, 11.14; $p = 0.01$) increase in systolic blood pressure. For the total UFP fraction, systolic blood pressure was 0.79 mmHg (95% CI: 0.07, 1.51; $p = 0.03$) higher, but no effects on systolic blood pressure were found for the nano-sized fractions with a diameter > 100 nm, nor PM_{2.5}, PM_{coarse}, and PM₁₀. Diastolic blood pressure was not associated with any of the studied particulate mass fractions.

Conclusion: Children attending school on days with higher UFP concentrations (diameter < 100 nm) had higher systolic blood pressure. The association was dependent on UFP size, and there was no association with the PM_{2.5} mass concentration.

Air Pollution and Lung Function in Dutch Children: A Comparison of Exposure Estimates and Associations Based on Land Use Regression and Dispersion Exposure Modeling Approaches

Meng Wang, Ulrike Gehring, Gerard Hoek, Menno Keuken, Sander Jonkers, Rob Beelen, Marloes Eeftens, Dirkje S. Postma, and Bert Brunekreef

123:847–851 (August 2015)

<http://dx.doi.org/10.1289/ehp.1408541>

Background: There is limited knowledge about the extent to which estimates of air pollution effects on health are affected by the choice for a specific exposure model.

Objectives: We aimed to evaluate the correlation between long-term air pollution exposure estimates using two commonly used exposure modeling techniques [dispersion and land use regression (LUR) models] and, in addition, to compare the estimates of the association between long-term exposure to air pollution and lung function in children using these exposure modeling techniques.

Methods: We used data of 1,058 participants of a Dutch birth cohort study with measured forced expiratory volume in 1 sec (FEV₁), forced vital capacity (FVC), and peak expiratory flow (PEF) measurements at 8 years of age. For each child, annual average outdoor air pollution exposure [nitrogen dioxide (NO₂), mass concentration of particulate matter with diameters ≤ 2.5 and ≤ 10 μm (PM_{2.5}, PM₁₀), and PM_{2.5} soot] was estimated for the current addresses of the participants by a dispersion and a LUR model. Associations between exposures to air pollution and lung function parameters were estimated using linear regression analysis with confounder adjustment.

Results: Correlations between LUR- and dispersion-modeled pollution concentrations were high for NO₂, PM_{2.5}, and PM_{2.5} soot ($R = 0.86$ – 0.90) but low for PM₁₀ ($R = 0.57$). Associations with lung function were similar for air pollutant exposures estimated using LUR and dispersion modeling, except for associations of PM_{2.5} with FEV₁ and FVC, which were stronger but less precise for exposures based on LUR compared with dispersion model.

Conclusions: Predictions from LUR and dispersion models correlated very well for PM_{2.5}, NO₂, and PM_{2.5} soot but not for PM₁₀. Health effect estimates did not depend on the type of model used to estimate exposure in a population of Dutch children.

Differences in Birth Weight Associated with the 2008 Beijing Olympics Air Pollution Reduction: Results from a Natural Experiment

David Q. Rich, Kaibo Liu, Jinliang Zhang, Sally W. Thurston, Timothy P. Stevens, Ying Pan, Cathleen Kane, Barry Weinberger, Pamela Ohman-Strickland, Tracey J. Woodruff, Xiaoli Duan, Vanessa Assibey-Mensah, and Junfeng Zhang

123:880–887 (September 2015)

<http://dx.doi.org/10.1289/ehp.1408795>

Background: Previous studies have reported decreased birth weight associated with increased air pollutant concentrations during pregnancy. However, it is not clear when during pregnancy increases in air pollution are associated with the largest differences in birth weight.

Objectives: Using the natural experiment of air pollution declines during the 2008 Beijing Olympics, we evaluated whether having specific months of pregnancy (i.e., 1st...8th) during the 2008 Olympics period was associated with larger birth weights, compared with pregnancies during the same dates in 2007 or 2009.

Methods: Using $n = 83,672$ term births to mothers residing in four urban districts of Beijing, we estimated the difference in birth weight associated with having individual months of pregnancy during the 2008 Olympics (8 August–24 September 2008) compared with the same dates in 2007 and 2009. We also estimated the difference in birth weight associated with interquartile range (IQR) increases in mean ambient particulate matter $\leq 2.5 \mu\text{m}$ in aerodynamic diameter ($\text{PM}_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO) concentrations during each pregnancy month.

Results: Babies whose 8th month of gestation occurred during the 2008 Olympics were, on average, 23 g larger (95% CI: 5 g, 40 g) than babies whose 8th month occurred during the same calendar dates in 2007 or 2009. IQR increases in $\text{PM}_{2.5}$ ($19.8 \mu\text{g}/\text{m}^3$), CO (0.3 ppm), SO_2 (1.8 ppb), and NO_2 (13.6 ppb) concentrations during the 8th month of pregnancy were associated with 18 g (95% CI: –32 g, –3 g), 17 g (95% CI: –28 g, –6 g), 23 g (95% CI: –36 g, –10 g), and 34 g (95% CI: –70 g, 3 g) decreases in birth weight, respectively. We did not see significant associations for months 1–7.

Conclusions: Short-term decreases in air pollution late in pregnancy in Beijing during the 2008 Summer Olympics, a normally heavily polluted city, were associated with higher birth weight.

» NEWS | SCIENCE SELECTION

Air Pollution and Birth Weight: New Clues about a Potential Critical Window of Exposure

Nancy Averett | A242 (September 2015)

<http://dx.doi.org/10.1289/ehp.123-A242>

ADVANCE PUBLICATION | Ambient Air Pollution and Newborn Size and Adiposity at Birth: Differences by Maternal Ethnicity (the Born in Bradford Study Cohort)

Anna Schembari, Kees de Hoogh, Marie Pedersen, Payam Dadvand, David Martinez, Gerard Hoek, Emily S. Petherick, John Wright, and Mark J. Nieuwenhuijsen

<http://dx.doi.org/10.1289/ehp.1408675>

ADVANCE PUBLICATION | Elemental Constituents of Particulate Matter and Newborn's Size in Eight European Cohorts

Marie Pedersen, Ulrike Gehring, Rob Beelen, Meng Wang, Lise Giorgis-Allemand, Anne-Marie Nybo Andersen, Xavier Basagaña, Claire Bernard, Marta Cirach, Francesco Forastiere, Kees de Hoogh, Regina Gražulevičienė, Olena Gruzieva, Gerard Hoek, Aleksandra Jedynska, Claudia Klümper, Ingeborg M. Kooter, Ursula Krämer, Jaakko Kukkonen, Daniela Porta, Dirkje S. Postma, Ole Raaschou-Nielsen, Lenie van Rossem, Jordi Sunyer, Mette Sørensen, Ming-Yi Tsai, Tanja G. M. Vrijkotte, Michael Wilhelm, Mark J. Nieuwenhuijsen, Göran Pershagen, Bert Brunekreef, Manolis Kogevinas, and Rémy Slama

<http://dx.doi.org/10.1289/ehp.1409546>

NATURAL GAS AND FRACKING

Proximity to Natural Gas Wells and Reported Health Status: Results of a Household Survey in Washington County, Pennsylvania

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123:21–26 (January 2015)

<http://dx.doi.org/10.1289/ehp.1307732>

Background: Little is known about the environmental and public health impact of unconventional natural gas extraction activities, including hydraulic fracturing, that occur near residential areas.

Objectives: Our aim was to assess the relationship between household proximity to natural gas wells and reported health symptoms.

Methods: We conducted a hypothesis-generating health symptom survey of 492 persons in 180 randomly selected households with ground-fed wells in an area of active natural gas drilling. Gas well proximity for each household was compared with the prevalence and frequency of reported dermal, respiratory, gastrointestinal, cardiovascular, and neurological symptoms.

Results: The number of reported health symptoms per person was higher among residents living < 1 km (mean \pm SD, 3.27 ± 3.72) compared with > 2 km from the nearest gas well (mean \pm SD, 1.60 ± 2.14 ; $p = 0.0002$). In a model that adjusted for age, sex, household education, smoking, awareness of environmental risk, work type, and animals in house, reported skin conditions were more common in households < 1 km compared with > 2 km from the nearest gas well (odds ratio = 4.1; 95% CI: 1.4, 12.3; $p = 0.01$). Upper respiratory symptoms were also more frequently reported in persons living in households < 1 km from gas wells (39%) compared with households 1–2 km or > 2 km from the nearest well (31 and 18%, respectively) ($p = 0.004$). No equivalent correlation was found between well proximity and other reported groups of respiratory, neurological, cardiovascular, or gastrointestinal conditions.

Conclusion: Although these results should be viewed as hypothesis generating, and the population studied was limited to households with a ground-fed water supply, proximity of natural gas wells may be associated with the prevalence of health symptoms including dermal and respiratory conditions in residents living near natural gas extraction activities. Further study of these associations, including the role of specific air and water exposures, is warranted.

ENDOTOXINS, FOOD TOXINS, AND WATER TOXINS

A Prospective Study of Growth and Biomarkers of Exposure to Aflatoxin and Fumonisin during Early Childhood in Tanzania

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123:173–178 (February 2015)

<http://dx.doi.org/10.1289/ehp.1408097>

Background: Aflatoxin and fumonisin are toxic food contaminants. Knowledge about effects of their exposure and coexposure on child growth is inadequate.

Objective: We investigated the association between child growth and aflatoxin and fumonisin exposure in Tanzania.

Methods: A total of 166 children were recruited at 6–14 months of age and studied at recruitment, and at the 6th and 12th month following recruitment. Blood and urine samples were collected and analyzed for plasma aflatoxin–albumin adducts (AF-alb) using ELISA, and urinary fumonisin B₁ (UFB1) using liquid chromatography–mass spectrometry, respectively. Anthropometric measurements were taken, and growth index z-scores were computed.

Results: AF-alb geometric mean concentrations (95% CIs) were 4.7 (3.9, 5.6), 12.9 (9.9, 16.7), and 23.5 (19.9, 27.7) pg/mg albumin at recruitment, 6 months, and 12 months from recruitment, respectively. At these respective sampling times, geometric mean UFB1 concentrations (95% CI) were 313.9 (257.4, 382.9), 167.3 (135.4, 206.7), and 569.5 (464.5, 698.2) pg/mL urine, and the prevalence of stunted children was 44%, 55%, and 56%, respectively. UFB1 concentrations at recruitment were negatively associated with length-for-age z-scores (LAZ) at 6 months ($p = 0.016$) and at 12 months from recruitment ($p = 0.014$). The mean UFB1 of the three sampling times (at recruitment and at 6 and 12 months from recruitment) in each child was negatively associated with LAZ ($p < 0.001$) and length velocity ($p = 0.004$) at 12 months from recruitment. The negative association between AF-alb and child growth did not reach statistical significance.

Conclusions: Exposure to fumonisin alone or coexposure with aflatoxins may contribute to child growth impairment.

CLIMATE CHANGE

Summertime Acute Heat Illness in U.S. Emergency Departments from 2006 through 2010: Analysis of a Nationally Representative Sample

Jeremy J. Hess, Shubhayu Saha, and George Luber

122:1209–1215 (November 2014)

<http://dx.doi.org/10.1289/ehp.1306796>

Background: Patients with acute heat illness present primarily to emergency departments (EDs), yet little is known regarding these visits.

Objective: We aimed to describe acute heat illness visits to U.S. EDs from 2006 through 2010 and identify factors associated with hospital admission or with death in the ED.

Methods: We extracted ED case-level data from the Nationwide Emergency Department Sample (NEDS) for 2006–2010, defining cases as ED visits from May through September with any heat illness diagnosis (ICD-9-CM 992.0–992.9). We correlated visit rates and temperature anomalies, analyzed demographics and ED disposition, identified risk factors for adverse outcomes, and examined ED case fatality rates (CFR).

Results: There were 326,497 (95% CI: 308,372, 344,658) cases, with 287,875 (88.2%) treated and released, 38,392 (11.8%) admitted, and 230 (0.07%) died in the ED. Heat illness diagnoses were first-listed in 68%. 74.7% had heat exhaustion, 5.4% heat stroke. Visit rates were highly correlated with annual temperature anomalies (Pearson correlation coefficient 0.882, $p = 0.005$). Treat-and-release rates were highest for younger adults (26.2/100,000/year), whereas hospitalization and death-in-the-ED rates were highest for older adults (6.7 and 0.03/100,000/year, respectively); all rates were highest in rural areas. Heat stroke had an ED CFR of 99.4/10,000 (95% CI: 78.7, 120.1) visits and was diagnosed in 77.0% of deaths. Adjusted odds of hospital admission or death in the ED were higher among elders, males, urban and low-income residents, and those with chronic conditions.

Conclusions: Heat illness presented to the ED frequently, with highest rates in rural areas. Case definitions should include all diagnoses. Visit rates were correlated with temperature anomalies. Heat stroke had a high ED CFR. Males, elders, and the chronically ill were at greatest risk of admission or death in the ED. Chronic disease burden exponentially increased this risk.

RELATED ARTICLES

FOCUS | A Hard Nut to Crack: Reducing Chemical Migration in Food-Contact Materials

Nate Seltenrich | A174 (July 2015)

<http://dx.doi.org/10.1289/ehp.123-A174>

Although food packaging serves important safety functions, these painstakingly engineered containers can also leach chemicals and other contaminants into the food and drink they protect. Researchers and food producers are searching for ways to stem this chemical migration, but solutions are proving elusive.



EDITORIAL | Protecting Our Children from Climate Change

Linda S. Birnbaum and Kimberly Thigpen Tart | A260 (October 2014)

<http://dx.doi.org/10.1289/ehp.1409165>

EDITORIAL | Jenny Pronczuk de Garbino: A Global Champion for Children's Health

Philip J. Landrigan and William A. Suk | A52 (March 2015)

<http://dx.doi.org/10.1289/ehp.1408293>

Ambient Heat and Sudden Infant Death: A Case-Crossover Study Spanning 30 Years in Montreal, Canada

Nathalie Auger, William D. Fraser, Audrey Smargiassi, and Tom Kosatsky

123:712–716 (July 2015)

<http://dx.doi.org/10.1289/ehp.1307960>

Background: Climate change may lead to more severe and extreme heat waves in the future, but its potential impact on sudden infant death—a leading cause of infant mortality—is unclear.

Objectives: We sought to determine whether risk of sudden infant death syndrome (SIDS) is elevated during hot weather.

Methods: We undertook a case-crossover analysis of all sudden infant deaths during warm periods in metropolitan Montreal, Quebec, Canada, from 1981 through 2010. Our analysis included a total of 196 certified cases of SIDS, including 89 deaths at 1–2 months of age, and 94 at 3–12 months. We estimated associations between maximum outdoor temperatures and SIDS by comparing outdoor temperatures on the day of or day before a SIDS event with temperatures on control days during the same month, using cubic splines to model temperature and adjusting for relative humidity.

Results: Maximum daily temperatures of $\geq 29^{\circ}\text{C}$ on the same day were associated with 2.78 times greater odds of sudden infant death relative to 20°C (95% CI: 1.64, 4.70). The likelihood of sudden death increased steadily with higher temperature. Associations were stronger for infants 3–12 months of age than for infants 1–2 months of age, with odds ratios of 3.90 (95% CI: 1.87, 8.13) and 1.73 (95% CI: 0.80, 3.73), respectively, for 29°C compared with 20°C on the day of the event.

Conclusions: High ambient temperature may be a novel risk factor for SIDS, especially at ≥ 3 months of age. Climate change and the higher temperatures that result may account for a potentially greater proportion of sudden infant deaths in the future.

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New Risk Factor for SIDS? Peaks in Cot Deaths Associated with Heat Waves

Carrie Arnold | A185 (July 2015)

<http://dx.doi.org/10.1289/ehp.123-A185>

RADIATION

Background Ionizing Radiation and the Risk of Childhood Cancer: A Census-Based Nationwide Cohort Study

Ben D. Spycher, Judith E. Lupatsch, Marcel Zwahlen, Martin Rösli, Felix Niggli, Michael A. Grotzer, Johannes Rischewski, Matthias Egger, and Claudia E. Kuehni for the Swiss Pediatric Oncology Group and the Swiss National Cohort Study Group

123:622–628 (June 2015)

<http://dx.doi.org/10.1289/ehp.1408548>

Background: Exposure to medium or high doses of ionizing radiation is a known risk factor for cancer in children. The extent to which low-dose radiation from natural sources contributes to the risk of childhood cancer remains unclear.

Objectives: In a nationwide census-based cohort study, we investigated whether the incidence of childhood cancer was associated with background radiation from terrestrial gamma and cosmic rays.

Methods: Children < 16 years of age in the Swiss National Censuses in 1990 and 2000 were included. The follow-up period lasted until 2008, and incident cancer cases were identified from the Swiss Childhood Cancer Registry. A radiation model was used to predict dose rates from terrestrial and cosmic radiation at locations of residence. Cox regression models were used to assess associations between cancer risk and dose rates and cumulative dose since birth.

Results: Among 2,093,660 children included at census, 1,782 incident cases of cancer were identified including 530 with leukemia, 328 with lymphoma, and 423 with a tumor of the central nervous system (CNS). Hazard ratios for each millisievert increase in cumulative dose of external radiation were 1.03 (95% CI: 1.01, 1.05) for any cancer, 1.04 (95% CI: 1.00, 1.08) for leukemia, 1.01 (95% CI: 0.96, 1.05) for lymphoma, and 1.04 (95% CI: 1.00, 1.08) for CNS tumors. Adjustment for a range of potential confounders had little effect on the results.

Conclusions: Our study suggests that background radiation may contribute to the risk of cancer in children, including leukemia and CNS tumors.

BUILT ENVIRONMENT

Residential Greenness and Birth Outcomes: Evaluating the Influence of Spatially Correlated Built-Environment Factors

Perry Hystad, Hugh W. Davies, Lawrence Frank, Josh Van Loon, Ulrike Gehring, Lillian Tamburic, and Michael Brauer

122:1095–1102 (October 2014)
<http://dx.doi.org/10.1289/ehp.1308049>

Background: Half the world's population lives in urban areas. It is therefore important to identify characteristics of the built environment that are beneficial to human health. Urban greenness has been associated with improvements in a diverse range of health conditions, including birth outcomes; however, few studies have attempted to distinguish potential effects of greenness from those of other spatially correlated exposures related to the built environment.

Objectives: We aimed to investigate associations between residential greenness and birth outcomes and evaluate the influence of spatially correlated built environment factors on these associations.

Methods: We examined associations between residential greenness [measured using satellite-derived Normalized Difference Vegetation Index (NDVI) within 100 m of study participants' homes] and birth outcomes in a cohort of 64,705 singleton births (from 1999–2002) in Vancouver, British Columbia, Canada. We also evaluated associations after adjusting for spatially correlated built environmental factors that may influence birth outcomes, including exposure to air pollution and noise, neighborhood walkability, and distance to the nearest park.

Results: An interquartile increase in greenness (0.1 in residential NDVI) was associated with higher term birth weight (20.6 g; 95% CI: 16.5, 24.7) and decreases in the likelihood of small for gestational age, very preterm (< 30 weeks), and moderately preterm (30–36 weeks) birth. Associations were robust to adjustment for air pollution and noise exposures, neighborhood walkability, and park proximity.

Conclusions: Increased residential greenness was associated with beneficial birth outcomes in this population-based cohort. These associations did not change after adjusting for other spatially correlated built environment factors, suggesting that alternative pathways (e.g., psychosocial and psychological mechanisms) may underlie associations between residential greenness and birth outcomes.

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Beyond Spatial Relationships: Residential Greenness and Birth Outcomes

Wendee Nicole | A281 (October 2014)
<http://dx.doi.org/10.1289/ehp.122-A281>

Risks and Benefits of Green Spaces for Children: A Cross-Sectional Study of Associations with Sedentary Behavior, Obesity, Asthma, and Allergy

Payam Dadvand, Cristina M. Villanueva, Laia Font-Ribera, David Martinez, Xavier Basagaña, Jordina Belmonte, Martine Vrijheid, Regina Gražulevičienė, Manolis Kogevinas, and Mark J. Nieuwenhuijsen

122:1329–1335 (December 2014)
<http://dx.doi.org/10.1289/ehp.1308038>

Background: Green spaces have been associated with both health benefits and risks in children; however, available evidence simultaneously investigating these conflicting influences, especially in association with different types of greenness, is scarce.

Objectives: We aimed to simultaneously evaluate health benefits and risks associated with different types of greenness in children, in terms of sedentary behavior (represented by excessive screen time), obesity, current asthma, and allergic rhinoconjunctivitis.

Methods: We conducted a cross-sectional study of a population-based sample of 3,178 schoolchildren (9–12 years old) in Sabadell, Spain, in 2006. Information on outcomes and covariates was obtained by questionnaire. We measured residential surrounding greenness as the average of satellite-derived Normalized Difference Vegetation Index (NDVI) in buffers of 100 m, 250 m, 500 m, and 1,000 m around each home address. Residential proximity to green spaces was defined as living within 300 m of a forest or a park, as separate variables. We used logistic regression models to estimate associations separately for each exposure–outcome pair, adjusted for relevant covariates.

Results: An interquartile range increase in residential surrounding greenness was associated with 11–19% lower relative prevalence of overweight/obesity and excessive screen time, but was not associated with current asthma and allergic rhinoconjunctivitis. Similarly, residential proximity to forests was associated with 39% and 25% lower relative prevalence of excessive screen time and overweight/obesity, respectively, but was not associated with current asthma. In contrast, living close to parks was associated with a 60% higher relative prevalence of current asthma, but had only weak negative associations with obesity/overweight or excessive screen time.

Conclusion: We observed two separable patterns of estimated health benefits and risks associated with different types of greenness.

Green and Blue Spaces and Behavioral Development in Barcelona Schoolchildren: The BREATHE Project

Elmira Amoly, Payam Dadvand, Joan Fornés, Mónica López-Vicente, Xavier Basagaña, Jordi Julvez, Mar Alvarez-Pedrerol, Mark J. Nieuwenhuijsen, and Jordi Sunyer

122:1351–1358 (December 2014)
<http://dx.doi.org/10.1289/ehp.1408215>

Background: Green spaces have been associated with improved mental health in children; however, available epidemiological evidence on their impact on child behavioral development is scarce.

Objectives: We investigated the impact of contact with green spaces and blue spaces (beaches) on indicators of behavioral development and symptoms of attention deficit/hyperactivity disorder (ADHD) in schoolchildren.

Methods: This study was based on a sample of 2,111 schoolchildren (7–10 years of age) from 36 schools in Barcelona in 2012. We obtained data on time spent in green spaces and beaches and Strengths and Difficulties Questionnaires (SDQ) from parents, and ADHD/DSM-IV questionnaires from teachers. Surrounding greenness was abstracted as the average Normalized Difference Vegetation Index (NDVI) in buffers of 100 m, 250 m, and 500 m around each home address. Proximity to green spaces was defined as living within 300 m of a major green space ($\geq 0.05 \text{ km}^2$). We applied quasi-Poisson mixed-effects models (with school random effect) to separately estimate associations between indicators of contact with green spaces and SDQ and ADHD total and subscale scores.

Results: We generally estimated beneficial associations between behavioral indicators and longer time spent in green spaces and beaches, and with residential surrounding greenness. Specifically, we found statistically significant inverse associations between green space playing time and SDQ total difficulties, emotional symptoms, and peer relationship problems; between residential surrounding greenness and SDQ total difficulties and hyperactivity/inattention and ADHD/DSM-IV total and inattention scores; and between annual beach attendance and SDQ total difficulties, peer relationship problems, and prosocial behavior. For proximity to major green spaces, the results were not conclusive.

Conclusion: Our findings support beneficial impacts of contact with green and blue spaces on behavioral development in schoolchildren.

Characteristics of Walkable Built Environments and BMI z-Scores in Children: Evidence from a Large Electronic Health Record Database

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122:1359–1365 (December 2014)
<http://dx.doi.org/10.1289/ehp.1307704>

Background: Childhood obesity remains a prominent public health problem. Walkable built environments may prevent excess weight gain.

Objectives: We examined the association of walkable built environment characteristics with body mass index (BMI) z-score among a large sample of children and adolescents.

Methods: We used geocoded residential address data from electronic health records of 49,770 children and adolescents 4 to < 19 years of age seen at the 14 pediatric practices of Harvard Vanguard Medical Associates from August 2011 through August 2012. We used eight geographic information system (GIS) variables to characterize walkable built environments. Outcomes were BMI z-score at the most recent visit and BMI z-score change from the earliest available (2008–2011) to the most recent (2011–2012) visit. Multivariable models were adjusted for child age, sex, race/ethnicity, and neighborhood median household income.

Results: In multivariable cross-sectional models, living in closer proximity to recreational open space was associated with lower BMI z-score. For example, children who lived in closest proximity (quartile 1) to the nearest recreational open space had a lower BMI z-score ($\beta = -0.06$; 95% CI: $-0.08, -0.03$) compared with those living farthest away (quartile 4; reference). Living in neighborhoods with fewer recreational open spaces and less residential density, traffic density, sidewalk completeness, and intersection density were associated with higher cross-sectional BMI z-score and with an increase in BMI z-score over time.

Conclusions: Overall, built environment characteristics that may increase walkability were associated with lower BMI z-scores in a large sample of children. Modifying existing built environments to make them more walkable may reduce childhood obesity.

Metro Nature, Environmental Health, and Economic Value

Kathleen L. Wolf and Alicia S.T. Robbins

123:390–398 (May 2015)

<http://dx.doi.org/10.1289/ehp.1408216>

Background: Nearly 40 years of research provides an extensive body of evidence about human health, well-being, and improved function benefits associated with experiences of nearby nature in cities.

Objectives: We demonstrate the numerous opportunities for future research efforts that link metro nature, human health and well-being outcomes, and economic values.

Methods: We reviewed the literature on urban nature-based health and well-being benefits. In this review, we provide a classification schematic and propose potential economic values associated with metro nature services.

Discussion: Economic valuation of benefits derived from urban green systems has largely been undertaken in the fields of environmental and natural resource economics, but studies have not typically addressed health outcomes. Urban trees, parks, gardens, open spaces, and other nearby nature elements—collectively termed metro nature—generate many positive externalities that have been largely overlooked in urban economics and policy. Here, we present a range of health benefits, including benefit context and beneficiaries. Although the understanding of these benefits is not yet consistently expressed, and although it is likely that attempts to link urban ecosystem services and economic values will not include all expressions of cultural or social value, the development of new interdisciplinary approaches that integrate environmental health and economic disciplines are greatly needed.

Conclusions: Metro nature provides diverse and substantial benefits to human populations in cities. In this review, we begin to address the need for development of valuation methodologies and new approaches to understanding the potential economic outcomes of these benefits.

GLOBAL HEALTH

Children's Health in Latin America: The Influence of Environmental Exposures

Amalia Laborde, Fernando Tomasina, Fabrizio Bianchi, Marie-Noel Bruné, Irena Buka, Pietro Comba, Lilian Corra, Liliana Cori, Christin Maria Duffert, Raul Harari, Ivano Iavarone, Melissa A. McDiarmid, Kimberly A. Gray, Peter D. Sly, Agnes Soares, William A. Suk, and Philip J. Landrigan

123:201–209 (March 2015)

<http://dx.doi.org/10.1289/ehp.1408292>

Background: Chronic diseases are increasing among children in Latin America.

Objective and Methods: To examine environmental risk factors for chronic disease in Latin American children and to develop a strategic initiative for control of these exposures, the World Health Organization (WHO) including the Pan American Health Organization (PAHO), the Collegium Ramazzini, and Latin American scientists reviewed regional and relevant global data.

Results: Industrial development and urbanization are proceeding rapidly in Latin America, and environmental pollution has become widespread. Environmental threats to children's health include traditional hazards such as indoor air pollution and drinking-water contamination; the newer hazards of urban air pollution; toxic chemicals such as lead, asbestos, mercury, arsenic, and pesticides; hazardous and electronic waste; and climate change. The mix of traditional and modern hazards varies greatly across and within countries reflecting industrialization, urbanization, and socioeconomic forces.

Conclusions: To control environmental threats to children's health in Latin America, WHO, including PAHO, will focus on the most highly prevalent and serious hazards—indoor and outdoor air pollution, water pollution, and toxic chemicals. Strategies for controlling these hazards include developing tracking data on regional trends in children's environmental health (CEH), building a network of Collaborating Centres, promoting biomedical research in CEH, building regional capacity, supporting development of evidence-based prevention policies, studying the economic costs of chronic diseases in children, and developing platforms for dialogue with relevant stakeholders.

» NEWS | SCIENCE SELECTION

Roadmap for Children's Health: Controlling Diverse Environmental Exposures in Latin America

Carol Potera | A70 (March 2015)

<http://dx.doi.org/10.1289/ehp.123-A70>

First Steps toward Harmonized Human Biomonitoring in Europe: Demonstration Project to Perform Human Biomonitoring on a European Scale

Elly Den Hond, Eva Govarts, Hanny Willems, Roel Smolders, Ludwine Casteleyn, Marike Kolossa-Gehring, Gerda Schwedler, Margarete Seiwert, Ulrike Fiddicke, Argelia Castaño, Marta Esteban, Jürgen Angerer, Holger M. Koch, Birgit K. Schindler, Ovnair Sepai, Karen Exley, Louis Bloemen, Milena Horvat, Lisbeth E. Knudsen, Anke Joas, Reinhard Joas, Pierre Biot, Dominique Aerts, Gudrun Koppen, Andromachi Katsonouri, Adamos Hadjipanayis, Andrea Krskova, Marek Maly, Thit A. Mørck, Peter Rudnai, Szilvia Kozepesy, Maurice Mulcahy, Rory Mannion, Arno C. Gutleb, Marc E. Fischer, Danuta Ligocka, Marek Jakubowski, M. Fátima Reis, Sónia Namorado, Anca Elena Gurzau, Ioana-Rodica Lupsa, Katarina Halzlova, Michal Jajcay, Darja Mazej, Janja Snoj Tratnik, Ana López, Estrella Lopez, Marika Berglund, Kristin Larsson, Andrea Lehmann, Pierre Crettaz, and Greet Schoeters

123:255–263 (March 2015)

<http://dx.doi.org/10.1289/ehp.1408616>

Background: For Europe as a whole, data on internal exposure to environmental chemicals do not yet exist. Characterization of the internal individual chemical environment is expected to enhance understanding of the environmental threats to health.

Objectives: We developed and applied a harmonized protocol to collect comparable human biomonitoring data all over Europe.

Methods: In 17 European countries, we measured mercury in hair and cotinine, phthalate metabolites, and cadmium in urine of 1,844 children (5–11 years of age) and their mothers. Specimens were collected over a 5-month period in 2011–2012. We obtained information on personal characteristics, environment, and lifestyle. We used the resulting database to compare concentrations of exposure biomarkers within Europe, to identify determinants of exposure, and to compare exposure biomarkers with health-based guidelines.

Results: Biomarker concentrations showed a wide variability in the European population. However, levels in children and mothers were highly correlated. Most biomarker concentrations were below the health-based guidance values.

Conclusions: We have taken the first steps to assess personal chemical exposures in Europe as a whole. Key success factors were the harmonized protocol development, intensive training and capacity building for field work, chemical analysis and communication, as well as stringent quality control programs for chemical and data analysis. Our project demonstrates the feasibility of a Europe-wide human biomonitoring framework to support the decision-making process of environmental measures to protect public health.

» NEWS | SCIENCE SELECTION

Continental Reference Point: Harmonized Human Biomonitoring across Europe

Kris Freeman | A71 (March 2015)

<http://dx.doi.org/10.1289/ehp.123-A71>

BIOMARKERS AND BIOMONITORING

Maternal Arsenic Exposure, Arsenic Methylation Efficiency, and Birth Outcomes in the Biomarkers of Exposure to ARsenic (BEAR) Pregnancy Cohort in Mexico

Jessica E. Laine, Kathryn A. Bailey, Marisela Rubio-Andrade, Andrew F. Olshan, Lisa Smeester, Zuzana Drobná, Amy H. Herring, Miroslav Stýblo, Gonzalo G. García-Vargas, and Rebecca C. Fry

123:186–192 (February 2015)
<http://dx.doi.org/10.1289/ehp.1307476>

Background: Exposure to inorganic arsenic (iAs) from drinking water is a global public health problem, yet much remains unknown about the extent of exposure in susceptible populations.

Objectives: We aimed to establish the Biomarkers of Exposure to ARsenic (BEAR) prospective pregnancy cohort in Gómez Palacio, Mexico, to better understand the effects of iAs exposure on pregnant women and their children.

Methods: Two hundred pregnant women were recruited for this study. Concentrations of iAs in drinking water (DW-iAs) and maternal urinary concentrations of iAs and its monomethylated and dimethylated metabolites (MMAs and DMAs, respectively) were determined. Birth outcomes were analyzed for their relationship to DW-iAs and to the concentrations and proportions of maternal urinary arsenicals.

Results: DW-iAs for the study subjects ranged from < 0.5 to 236 µg As/L. More than half of the women (53%) had DW-iAs that exceeded the World Health Organization's recommended guideline of 10 µg As/L. DW-iAs was significantly associated with the sum of the urinary arsenicals (U-tAs). Maternal urinary concentrations of MMAs were negatively associated with newborn birth weight and gestational age. Maternal urinary concentrations of iAs were associated with lower mean gestational age and newborn length.

Conclusions: Biomonitoring results demonstrate that pregnant women in Gómez Palacio are exposed to potentially harmful levels of DW-iAs. The data support a relationship between iAs metabolism in pregnant women and adverse birth outcomes. The results underscore the risks associated with iAs exposure in vulnerable populations.

Urinary Phthalate Metabolites and Biomarkers of Oxidative Stress in Pregnant Women: A Repeated Measures Analysis

Kelly K. Ferguson, Thomas F. McElrath, Yin-Hsiu Chen, Bhramar Mukherjee, and John D. Meeker

123:210–216 (March 2015)
<http://dx.doi.org/10.1289/ehp.1307996>

Background: Phthalate exposure occurs readily in the environment and has been associated with an array of health end points, including adverse birth outcomes. Some of these may be mediated by oxidative stress, a proposed mechanism for phthalate action.

Objectives: In the present study, we explored the associations between phthalate metabolites and biomarkers of oxidative stress measured in urine samples from multiple time points during pregnancy.

Methods: Women were participants in a nested case–control study of preterm birth ($n = 130$ cases, $n = 352$ controls). Each was recruited early in pregnancy and followed until delivery, providing urine samples at up to four visits. Nine phthalate metabolites were measured to assess exposure, and 8-hydroxydeoxyguanosine and 8-isoprostane were also measured in urine as markers of oxidative stress. Associations were assessed using linear mixed models to account for intraindividual correlation, with inverse selection probability weightings based on case status to allow for greater generalizability.

Results: Interquartile range increases in phthalate metabolites were associated with significantly higher concentrations of both biomarkers. Estimated differences were greater in association with monobenzyl phthalate (MBzP), mono-*n*-butyl phthalate (MBP), and monoisobutyl phthalate (MiBP), compared with di(2-ethylhexyl) phthalate (DEHP) metabolites.

Conclusions: Urinary phthalate metabolites were associated with increased oxidative stress biomarkers in our study population of pregnant women. These relationships may be particularly relevant to the study of birth outcomes linked to phthalate exposure. Although replication is necessary in other populations, these results may also be of great importance for a range of other health outcomes associated with phthalates.

Methodologies and Populations

Variation in Urinary Flow Rates According to Demographic Characteristics and Body Mass Index in NHANES: Potential Confounding of Associations between Health Outcomes and Urinary Biomarker Concentrations

Sean M. Hays, Lesa L. Aylward, and Benjamin C. Blount

123:293–300 (April 2015)

<http://dx.doi.org/10.1289/ehp.1408944>

Background: Urinary analyte concentrations are affected both by exposure level and by urinary flow rate (UFR). Systematic variations in UFR with demographic characteristics or body mass index (BMI) could confound assessment of associations between health outcomes and biomarker concentrations.

Objectives: We assessed patterns of UFR (milliliters per hour) and body weight–adjusted UFR (UFRBW; milliliters per kilogram per hour) across age, sex, race/ethnicity, and BMI category in the NHANES (National Health and Nutrition Examination Survey) 2009–2012 data sets.

Methods: Geometric mean (GM) UFR and UFRBW were compared across age-stratified (6–11, 12–19, 20–39, 40–59, and ≥ 60 years) subgroups (sex, race/ethnicity, and BMI category). Patterns of analyte urinary concentration or mass excretion rates (nanograms per hour and nanograms per kilogram per hour BW) were assessed in sample age groups for case study chemicals bisphenol A and 2,5-dichlorophenol.

Results: UFR increased from ages 6 to 60 years and then declined with increasing age. UFRBW varied inversely with age. UFR, but not UFRBW, differed significantly by sex (males > females after age 12 years). Differences in both metrics were observed among categories of race/ethnicity. UFRBW, but not UFR, varied inversely with BMI category and waist circumference in all age groups. Urinary osmolality increased with increasing BMI. Case studies demonstrated different exposure–outcome relationships depending on exposure metric. Conventional hydration status adjustments did not fully address the effect of flow rate variations.

Conclusions: UFR and UFRBW exhibit systematic variations with age, sex, race/ethnicity, and BMI category. These variations can confound assessments of potential exposure–health outcome associations based on urinary concentration. Analyte excretion rates are valuable exposure metrics in such assessments.

» NEWS | SCIENCE SELECTION

Urinary Biomarkers as Exposure Surrogates: Controlling for Possible Bias

Julia R. Barrett | A97 (April 2015)

<http://dx.doi.org/10.1289/ehp.123-A97>

EPIGENETICS

Identification of DNA Methylation Changes in Newborns Related to Maternal Smoking during Pregnancy

Christina A. Markunas, Zongli Xu, Sophia Harlid, Paul A. Wade, Rolv T. Lie, Jack A. Taylor, and Allen J. Wilcox

122:1147–1153 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307892>

Background: Maternal smoking during pregnancy is associated with significant infant morbidity and mortality, and may influence later disease risk. One mechanism by which smoking (and other environmental factors) might have long-lasting effects is through epigenetic modifications such as DNA methylation.

Objectives: We conducted an epigenome-wide association study (EWAS) investigating alterations in DNA methylation in infants exposed *in utero* to maternal tobacco smoke, using the Norway Facial Clefts Study.

Methods: The Illumina HumanMethylation450 BeadChip was used to assess DNA methylation in whole blood from 889 infants shortly after delivery. Of 889 mothers, 287 reported smoking—twice as many smokers as in any previous EWAS of maternal smoking. CpG sites related to maternal smoking during the first trimester were identified using robust linear regression.

Results: We identified 185 CpGs with altered methylation in infants of smokers at genome-wide significance (q -value < 0.05; mean $\Delta\beta = \pm 2\%$). These correspond to 110 gene regions, of which 7 have been previously reported and 10 are newly confirmed using publicly available results. Among these 10, the most noteworthy are *FRMD4A*, *ATP9A*, *GALNT2*, and *MEG3*, implicated in processes related to nicotine dependence, smoking cessation, and placental and embryonic development.

Conclusions: Our study identified 10 genes with newly established links to maternal smoking. Further, we note differences between smoking-related methylation changes in newborns and adults, suggesting possible distinct effects of direct versus indirect tobacco smoke exposure as well as potential differences due to age. Further work would be needed to determine whether these small changes in DNA methylation are biologically or clinically relevant. The methylation changes identified in newborns may mediate the association between *in utero* maternal smoking exposure and later health outcomes.

Methodologies and Populations

Prenatal Exposure to Maternal Cigarette Smoking and DNA Methylation: Epigenome-Wide Association in a Discovery Sample of Adolescents and Replication in an Independent Cohort at Birth through 17 Years of Age

Ken W.K. Lee, Rebecca Richmond, Pingzhao Hu, Leon French, Jean Shin, Celine Bourdon, Eva Reischl, Melanie Waldenberger, Sonja Zeilinger, Tom Gaunt, Wendy McArdle, Susan Ring, Geoff Woodward, Luigi Bouchard, Daniel Gaudet, George Davey Smith, Caroline Relton, Tomas Paus, and Zdenka Pausova

123:193–199 (February 2015)

<http://dx.doi.org/10.1289/ehp.1408614>

Background: Prenatal exposure to maternal cigarette smoking (prenatal smoke exposure) had been associated with altered DNA methylation (DNAm) at birth.

Objective: We examined whether such alterations are present from birth through adolescence.

Methods: We used the Infinium HumanMethylation450K BeadChip to search across 473,395 CpGs for differential DNAm associated with prenatal smoke exposure during adolescence in a discovery cohort ($n = 132$) and at birth, during childhood, and during adolescence in a replication cohort ($n = 447$).

Results: In the discovery cohort, we found five CpGs in *MYO1G* (top-ranking CpG: cg12803068, $p = 3.3 \times 10^{-11}$) and *CNTNAP2* (cg25949550, $p = 4.0 \times 10^{-9}$) to be differentially methylated between exposed and nonexposed individuals during adolescence. The CpGs in *MYO1G* and *CNTNAP2* were associated, respectively, with higher and lower DNAm in exposed versus nonexposed adolescents. The same CpGs were differentially methylated at birth, during childhood, and during adolescence in the replication cohort. In both cohorts and at all developmental time points, the differential DNAm was in the same direction and of a similar magnitude, and was not altered appreciably by adjustment for current smoking by the participants or their parents. In addition, four of the five EWAS (epigenome-wide association study)–significant CpGs in the adolescent discovery cohort were also among the top sites of differential methylation in a previous birth cohort, and differential methylation of CpGs in *CYP1A1*, *AHRR*, and *GFI1* observed in that study was also evident in our discovery cohort.

Conclusions: Our findings suggest that modifications of DNAm associated with prenatal maternal smoking may persist in exposed offspring for many years—at least until adolescence.

Environmental, Dietary, Maternal, and Fetal Predictors of Bulky DNA Adducts in Cord Blood: A European Mother–Child Study (NewGeneris)

Marie Pedersen, Michelle A. Mendez, Bernadette Schoket, Roger W. Godschalk, Ana Espinosa, Anette Landström, Cristina M. Villanueva, Domenico F. Merlo, Eleni Fthenou, Esther Gracia-Lavedan, Frederik-J. van Schooten, Gerard Hoek, Gunnar Brunborg, Helle M. Meltzer, Jan Alexander, Jeanette K. Nielsen, Jordi Sunyer, John Wright, Katalin Kovács, Kees de Hoogh, Kristine B. Gutzkow, Laura J. Hardie, Leda Chatzi, Lisbeth E. Knudsen, Livia Anna, Matthias Ketzel, Margaretha Haugen, Maria Botsivali, Mark J. Nieuwenhuijsen, Marta Cirach, Mireille B. Toledano, Rachel B. Smith, Sarah Fleming, Silvia Agramunt, Soterios A. Kyrtopoulos, Viktória Lukács, Jos C. Kleinjans, Dan Segerbäck, and Manolis Kogevinas

123:374–380 (April 2015)

<http://dx.doi.org/10.1289/ehp.1408613>

Background: Bulky DNA adducts reflect genotoxic exposures, have been associated with lower birth weight, and may predict cancer risk.

Objective: We selected factors known or hypothesized to affect *in utero* adduct formation and repair and examined their associations with adduct levels in neonates.

Methods: Pregnant women from Greece, Spain, England, Denmark, and Norway were recruited in 2006–2010. Cord blood bulky DNA adduct levels were measured by the ^{32}P -postlabeling technique ($n = 511$). Diet and maternal characteristics were assessed via questionnaires. Modeled exposures to air pollutants and drinking-water disinfection by-products, mainly trihalomethanes (THMs), were available for a large proportion of the study population.

Results: Greek and Spanish neonates had higher adduct levels than the northern European neonates [median, 12.1 ($n = 179$) vs. 6.8 ($n = 332$) adducts per 108 nucleotides, $p < 0.001$]. Residence in southern European countries, higher maternal body mass index, delivery by cesarean section, male infant sex, low maternal intake of fruits rich in vitamin C, high intake of dairy products, and low adherence to healthy diet score were statistically significantly associated with higher adduct levels in adjusted models. Exposure to fine particulate matter and nitrogen dioxide was associated with significantly higher adducts in the Danish subsample only. Overall, the pooled results for THMs in water show no evidence of association with adduct levels; however, there are country-specific differences in results with a suggestion of an association in England.

Conclusion: These findings suggest that a combination of factors, including unknown country-specific factors, influence the bulky DNA adduct levels in neonates.

Methodologies and Populations

Placental DNA Methylation Related to Both Infant Toenail Mercury and Adverse Neurobehavioral Outcomes

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123:723–729 (July 2015)

<http://dx.doi.org/10.1289/ehp.1408561>

Background: Prenatal mercury (Hg) exposure is associated with adverse child neurobehavioral outcomes. Because Hg can interfere with placental functioning and cross the placenta to target the fetal brain, prenatal Hg exposure can inhibit fetal growth and development directly and indirectly.

Objectives: We examined potential associations between prenatal Hg exposure assessed through infant toenail Hg, placental DNA methylation changes, and newborn neurobehavioral outcomes.

Methods: The methylation status of > 485,000 CpG loci was interrogated in 192 placental samples using Illumina's Infinium HumanMethylation450 BeadArray. Hg concentrations were analyzed in toenail clippings from a subset of 41 infants; neurobehavior was assessed using the NICU Network Neurobehavioral Scales (NNNS) in an independent subset of 151 infants.

Results: We identified 339 loci with an average methylation difference > 0.125 between any two toenail Hg tertiles. Variation among these loci was subsequently found to be associated with a high-risk neurodevelopmental profile (omnibus p -value = 0.007) characterized by the NNNS. Ten loci had $p < 0.01$ for the association between methylation and the high-risk NNNS profile. Six of 10 loci reside in the *EMID2* gene and were hypomethylated in the 16 high-risk profile infants' placentas. Methylation at these loci was moderately correlated (correlation coefficients range, –0.33 to –0.45) with *EMID2* expression.

Conclusions: *EMID2* hypomethylation may represent a novel mechanism linking *in utero* Hg exposure and adverse infant neurobehavioral outcomes.

In Utero Fine Particle Air Pollution and Placental Expression of Genes in the Brain-Derived Neurotrophic Factor Signaling Pathway: An ENVIRONAGE Birth Cohort Study

Nelly D. Saenen, Michelle Plusquin, Esmée Bijlens, Bram G. Janssen, Wilfried Gyselaers, Bianca Cox, Frans Fierens, Geert Molenberghs, Joris Penders, Karen Vrijens, Patrick De Boever, and Tim S. Nawrot

123:834–840 (August 2015)

<http://dx.doi.org/10.1289/ehp.1408549>

Background: Developmental processes in the placenta and the fetal brain are shaped by the same biological signals. Recent evidence suggests that adaptive responses of the placenta to the maternal environment may influence central nervous system development.

Objectives: We studied the association between *in utero* exposure to fine particle air pollution with a diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and placental expression of genes implicated in neural development.

Methods: Expression of 10 target genes in the brain-derived neurotrophic factor (*BDNF*) signaling pathway were quantified in placental tissue of 90 mother–infant pairs from the ENVIRONAGE birth cohort using quantitative real-time polymerase chain reaction. Trimester-specific $\text{PM}_{2.5}$ exposure levels were estimated for each mother's home address using a spatiotemporal model. Mixed-effects models were used to evaluate the association between the target genes and $\text{PM}_{2.5}$ exposure measured in different time windows of pregnancy.

Results: A $5\text{-}\mu\text{g}/\text{m}^3$ increase in residential $\text{PM}_{2.5}$ exposure during the first trimester of pregnancy was associated with a 15.9% decrease [95% confidence interval (CI): –28.7, –3.2%, $p = 0.015$] in expression of placental *BDNF* at birth. The corresponding estimate for synapsin 1 (*SYN1*) was a 24.3% decrease (95% CI: –42.8, –5.8%, $p = 0.011$).

Conclusions: Placental expression of *BDNF* and *SYN1*, two genes implicated in normal neurodevelopmental trajectories, decreased with increasing *in utero* exposure to $\text{PM}_{2.5}$. Future studies are needed to confirm our findings and evaluate the potential relevance of associations between $\text{PM}_{2.5}$ and placental expression of *BDNF* and *SYN1* on neurodevelopment. We provide the first molecular epidemiological evidence concerning associations between *in utero* fine particle air pollution exposure and the expression of genes that may influence neurodevelopmental processes.

METHODOLOGIES

The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes

Tracey J. Woodruff and Patrice Sutton

122:1007–1014 (October 2014)
<http://dx.doi.org/10.1289/ehp.1307175>

Background: Synthesizing what is known about the environmental drivers of health is instrumental to taking prevention-oriented action. Methods of research synthesis commonly used in environmental health lag behind systematic review methods developed in the clinical sciences over the past 20 years.

Objectives: We sought to develop a proof of concept of the “Navigation Guide,” a systematic and transparent method of research synthesis in environmental health.

Discussion: The Navigation Guide methodology builds on best practices in research synthesis in evidence-based medicine and environmental health. Key points of departure from current methods of expert-based narrative review prevalent in environmental health include a prespecified protocol, standardized and transparent documentation including expert judgment, a comprehensive search strategy, assessment of “risk of bias,” and separation of the science from values and preferences. Key points of departure from evidence-based medicine include assigning a “moderate” quality rating to human observational studies and combining diverse evidence streams.

Conclusions: The Navigation Guide methodology is a systematic and rigorous approach to research synthesis that has been developed to reduce bias and maximize transparency in the evaluation of environmental health information. Although novel aspects of the method will require further development and validation, our findings demonstrated that improved methods of research synthesis under development at the National Toxicology Program and under consideration by the U.S. Environmental Protection Agency are fully achievable. The institutionalization of robust methods of systematic and transparent review would provide a concrete mechanism for linking science to timely action to prevent harm.

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth

Erica Koustas, Juleen Lam, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff

122:1015–1027 (October 2014)
<http://dx.doi.org/10.1289/ehp.1307177>

Background: In contrast to current methods of expert-based narrative review, the Navigation Guide is a systematic and transparent method for synthesizing environmental health research from multiple evidence streams. The Navigation Guide was developed to effectively and efficiently translate the available scientific evidence into timely prevention-oriented action.

Objectives: We applied the Navigation Guide systematic review method to answer the question “Does fetal developmental exposure to perfluorooctanoic acid (PFOA) or its salts affect fetal growth in animals?” and to rate the strength of the experimental animal evidence.

Methods: We conducted a comprehensive search of the literature, applied prespecified criteria to the search results to identify relevant studies, extracted data from studies, obtained additional information from study authors, conducted meta-analyses, and rated the overall quality and strength of the evidence.

Results: Twenty-one studies met the inclusion criteria. From the meta-analysis of eight mouse gavage data sets, we estimated that exposure of pregnant mice to increasing concentrations of PFOA was associated with a change in mean pup birth weight of -0.023 g (95% CI: -0.029 , -0.016) per 1-unit increase in dose (milligrams per kilogram body weight per day). The evidence, consisting of 15 mammalian and 6 nonmammalian studies, was rated as “moderate” and “low” quality, respectively.

Conclusion: Based on this first application of the Navigation Guide methodology, we found sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.

Methodologies and Populations

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth

Paula I. Johnson, Patrice Sutton, Dylan S. Atchley, Erica Koustas, Juleen Lam, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff

122:1028–1039 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307893>

Background: The Navigation Guide methodology was developed to meet the need for a robust method of systematic and transparent research synthesis in environmental health science. We conducted a case study systematic review to support proof of concept of the method.

Objective: We applied the Navigation Guide systematic review methodology to determine whether developmental exposure to perfluorooctanoic acid (PFOA) affects fetal growth in humans.

Methods: We applied the first 3 steps of the Navigation Guide methodology to human epidemiological data: 1) specify the study question, 2) select the evidence, and 3) rate the quality and strength of the evidence. We developed a protocol, conducted a comprehensive search of the literature, and identified relevant studies using prespecified criteria. We evaluated each study for risk of bias and conducted meta-analyses on a subset of studies. We rated quality and strength of the entire body of human evidence.

Results: We identified 18 human studies that met our inclusion criteria, and 9 of these were combined through meta-analysis. Through meta-analysis, we estimated that a 1-ng/mL increase in serum or plasma PFOA was associated with a –18.9 g (95% CI: –29.8, –7.9) difference in birth weight. We concluded that the risk of bias across studies was low, and we assigned a “moderate” quality rating to the overall body of human evidence.

Conclusion: On the basis of this first application of the Navigation Guide systematic review methodology, we concluded that there is “sufficient” human evidence that developmental exposure to PFOA reduces fetal growth.

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth

Juleen Lam, Erica Koustas, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff

122:1040–1051 (October 2014)

<http://dx.doi.org/10.1289/ehp.1307923>

Background: The Navigation Guide is a novel systematic review method to synthesize scientific evidence and reach strength of evidence conclusions for environmental health decision making.

Objective: Our aim was to integrate scientific findings from human and nonhuman studies to determine the overall strength of evidence for the question “Does developmental exposure to perfluorooctanoic acid (PFOA) affect fetal growth in humans?”

Methods: We developed and applied prespecified criteria to systematically and transparently a) rate the quality of the scientific evidence as “high,” “moderate,” or “low”; b) rate the strength of the human and nonhuman evidence separately as “sufficient,” “limited,” “moderate,” or “evidence of lack of toxicity”; and c) integrate the strength of the human and nonhuman evidence ratings into a strength of the evidence conclusion.

Results: We identified 18 epidemiology studies and 21 animal toxicology studies relevant to our study question. We rated both the human and nonhuman mammalian evidence as “moderate” quality and “sufficient” strength. Integration of these evidence ratings produced a final strength of evidence rating in which review authors concluded that PFOA is “known to be toxic” to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.

Conclusion: We concluded that developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species. The results of this case study demonstrate the application of a systematic and transparent methodology, via the Navigation Guide, for reaching strength of evidence conclusions in environmental health.

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The Navigation Guide: Systematic Review for the Environmental Health Sciences

Julia R. Barrett | A283 (October 2014)

<http://dx.doi.org/10.1289/ehp.122-A283>

Methodologies and Populations

Examination of the Safety of Pediatric Vaccine Schedules in a Non-Human Primate Model: Assessments of Neurodevelopment, Learning, and Social Behavior

Britni Curtis, Noelle Liberato, Megan Rulien, Kelly Morrisroe, Caroline Kenney, Vernon Yutuc, Clayton Ferrier, C. Nathan Marti, Dorothy Mandell, Thomas M. Burbacher, Gene P. Sackett, and Laura Hewitson

123:579–589 (June 2015)

<http://dx.doi.org/10.1289/ehp.1408257>

Background: In the 1990s, the mercury-based preservative thimerosal was used in most pediatric vaccines. Although there are currently only two thimerosal-containing vaccines (TCVs) recommended for pediatric use, parental perceptions that vaccines pose safety concerns are affecting vaccination rates, particularly in light of the much expanded and more complex schedule in place today.

Objectives: The objective of this study was to examine the safety of pediatric vaccine schedules in a non-human primate model.

Methods: We administered vaccines to six groups of infant male rhesus macaques ($n = 12$ – 16 /group) using a standardized thimerosal dose where appropriate. Study groups included the recommended 1990s Pediatric vaccine schedule, an accelerated 1990s Primate schedule with or without the measles–mumps–rubella (MMR) vaccine, the MMR vaccine only, and the expanded 2008 schedule. We administered saline injections to age-matched control animals ($n = 16$). Infant development was assessed from birth to 12 months of age by examining the acquisition of neonatal reflexes, the development of object concept permanence (OCP), computerized tests of discrimination learning, and infant social behavior. Data were analyzed using analysis of variance, multilevel modeling, and survival analyses, where appropriate.

Results: We observed no group differences in the acquisition of OCP. During discrimination learning, animals receiving TCVs had improved performance on reversal testing, although some of these same animals showed poorer performance in subsequent learning-set testing. Analysis of social and nonsocial behaviors identified few instances of negative behaviors across the entire infancy period. Although some group differences in specific behaviors were reported at 2 months of age, by 12 months all infants, irrespective of vaccination status, had developed the typical repertoire of macaque behaviors.

Conclusions: This comprehensive 5-year case–control study, which closely examined the effects of pediatric vaccines on early primate development, provided no consistent evidence of neurodevelopmental deficits or aberrant behavior in vaccinated animals.

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Pediatric Vaccines and Neurodevelopment: Primate Study Finds No Adverse Behavioral Effects

Julia R. Barrett | A156 (June 2015)

<http://dx.doi.org/10.1289/ehp.123-A156>

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